

Methamphetamine-Induced Pulmonary Arterial Hypertension is Associated with Worse Right Ventricular Function

Bon LI*, Maksimovich NYe and Sivitsky DV

Grodno State Medical University, Gorkogo St, Grodno, Republic of Belarus.

*Correspondence:

Bon LI, Candidate of Biological Science, Assistant Professor of Pathophysiology Department named D. A. Maslakov, Grodno State Medical University; Grodno State Medical University, Grodno, Belarus.

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a progressive and life-threatening disease characterized by irreversible pulmonary vascular remodeling, ultimately leading to right heart failure, hemodynamic instability, and death. Although numerous risk factors for the development of PAH have been described, methamphetamine-associated PAH (MA-PAH) has gained increasing recognition in recent years. Emerging data suggest significant differences in functional class, morbidity, and mortality in patients with MA-PAH compared to other forms of the disease, necessitating a reconsideration of risk stratification approaches in this cohort [1].

Methamphetamine is a highly addictive psychostimulant whose prevalence in the United States has increased dramatically, with an overall increase of 43% from 2015 to 2019, while non-drug (non-injection) use increased by 105% over the same period [2]. Only recently has methamphetamine been recognized as an independent risk factor for the development of PAH. Studies have shown that stimulant use is ten times more common among patients with idiopathic PAH (I-PAH) compared to patients with other established risk factors [3,4]. The pathophysiological mechanisms by which methamphetamine induces PAH remain incompletely understood. Proposed mechanisms include direct toxic injury to the pulmonary vascular wall, oxidative stress, dysregulation of the pulmonary vasodilator-to-vasoconstrictor ratio, and decreased activity of carboxylesterase 1 (CES1), an enzyme involved in drug and xenobiotic metabolism [5-7].

Retrospective analyses convincingly demonstrate that patients with I-PAH have a more severe functional class and a worse prognosis compared to other types of precapillary pulmonary hypertension. In a study by Charoenpong et al. involving 1830 patients from the PAH Biobank, mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) were higher in individuals with MA-PAH than in patients with PAH associated with connective tissue diseases (although no significant differences were observed from I-PAH) [8]. Data from the Pulmonary Hypertension Association Registry revealed that patients with MA-PAH have a lower cardiac index and a higher hospitalization rate than patients with I-PAH, while their functional status is generally worse [9]. A prospective cohort study conducted at the Stanford University Pulmonary Hypertension Program showed that patients with MA-PAH suffer from more severe heart failure symptoms compared to patients with I-PAH [1]. Moreover, Ramirez et al. presented evidence that, despite ongoing therapy, patients with MA-PAH have a lower 5-year survival rate, as well as worse functional status and exercise tolerance [10].

Echocardiography is an integral non-invasive screening method for pulmonary hypertension and is widely used to assess prognosis and monitor the effectiveness of therapy in PAH [11]. Numerous studies have confirmed the prognostic significance of right atrial (RA) mechanics, including RA ejection fraction, RA emptying fraction, RA size, and right ventricular outflow tract velocity integral, in determining the prognosis of pulmonary hypertension [12-14]. In recent years, the role of right atrial and right ventricular strain has been actively studied using speckle-tracking echocardiography for risk stratification and disease prognosis [15,16]. Echocardiographic gating allows one to assess the degree of myocardial deformation during contraction and provides unique information about subclinical myocardial dysfunction, which is not detected by standard

echocardiographic measurements. In patients with pulmonary hypertension, right atrial reservoir gating is significantly reduced compared to controls; this reduction is associated with clinical deterioration and is an independent predictor of 5-year mortality [15,17-19]. Furthermore, it has been shown that right atrial and right ventricular gating worsen even before the development of a significant decrease in right ventricular ejection fraction, indicating the presence of subclinical right heart dysfunction [16].

Keywords

Pulmonary arterial hypertension, Methamphetamine-associated pulmonary arterial hypertension, Idiopathic pulmonary arterial hypertension, Right heart remodeling, Right atrial straight, Right ventricular free wall straight, Speckle-tracking echocardiography, Subclinical myocardial dysfunction, Hemodynamics, Risk stratification.

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by pulmonary vascular remodeling and subsequent right ventricular failure, hemodynamic instability, and death. Although numerous known risk factors are associated with the development of PAH, methamphetamine-associated PAH (methamphetamine-associated PAH) is increasingly recognized as having a unique impact on patient risk stratification due to emerging data indicating significant differences in functional class, morbidity, and mortality [1].

Methamphetamine is a highly addictive substance whose use in the United States has increased significantly, increasing by 43% between 2015 and 2019, with non-injection methamphetamine use increasing by a staggering 105% over the same period [2]. Methamphetamine has only recently been recognized as an independent risk factor for PAH, with studies in patients with idiopathic PAH (I-PAH) showing a tenfold association with stimulant use compared to PAH patients with known risk factors [3,4]. Although the mechanism by which methamphetamine use leads to PAH is unclear, proposed mechanisms include direct pulmonary toxicity and vascular injury, oxidative stress, dysregulation of pulmonary vasodilators and vasoconstrictors, and decreased activity of CES1, a serine esterase involved in drug metabolism [5-7].

Retrospective analyses show that individuals with MA-PAH have a worse functional class and prognosis compared with other types of precapillary pulmonary hypertension (PPH). In their study of 1,830 patients included in the PAH Biobank, Charoenpong et al. found that mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) were higher in individuals with MA-PAH than in those with CTD-PAH (although not significantly different from I-PAH) [8]. Data from the Pulmonary Hypertension Association Registry showed that patients with MA-PAH have a lower cardiac index than patients with I-PAH and are more frequently hospitalized, while their functional status is generally worse [9]. A prospective cohort study of patients with MA-PAH and I-PAH referred to the Stanford University Pulmonary Hypertension Program found that patients with MA-PAH had more severe heart failure symptoms [1]. Ramirez et al. found evidence that, despite therapy, patients with MA-PAH have

lower 5-year survival and also experience worse functional status and exercise capacity [10].

Echocardiography is an integral non-invasive method for screening pulmonary hypertension and is also used to assess prognosis and monitor the effectiveness of therapy in PAH [11]. Numerous 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, in establishing prognostic implications in PH [12-14]. More recent work has investigated the role of RA and RV strain using speckle tracking echocardiography in PH for its use in risk stratification and prognosis [15,16]. Echocardiographic strain is an assessment of myocardial distortion during contraction and provides valuable information about subclinical myocardial dysfunction. In patients with LPH, right atrial strain has been shown to be significantly reduced compared with controls, which is associated with clinical deterioration and is an independent predictor of 5-year mortality [15-19]. Right atrial and right ventricular strain have also been shown to worsen in LPH before the onset of marked reduction in FEP, indicating subclinical right heart dysfunction [16]. Previous studies have demonstrated the importance of assessing right heart strain for identifying subclinical right heart dysfunction and prognosticating pulmonary hypertension. In this study, we examined whether echocardiographic indices of right heart function, including right heart strain, could provide insight into the mechanism underlying the worse prognosis observed in individuals with MA-PAH compared to I-PAH [20].

Patient Contingent

Patient population Patients diagnosed with pulmonary hypertension previously followed by the University of Utah Pulmonary Hypertension Program were retrospectively included in a registry established specifically for this program between August 2020 and December 2021. A matching method was used to exclude the influence of pulmonary artery pressure on right heart function, since elevated pulmonary artery pressure represents an increase in right ventricular afterload and leads to right heart strain and failure [21]. In this study, we retrospectively included 51 patients with MA-PAH matched by mean pulmonary artery pressure (mPAP) with 51 patients with I-PAH. PAH was defined as mPAP > 20 mmHg and pulmonary capillary wedge pressure (PCWP) less than or equal to 18 mmHg based on right heart catheterization [3]. Inclusion criteria for the registry were based on a previously established diagnosis using criteria similar to those of the Registry for the Evaluation of Early and Long-Term Care of PAH (REVEAL) or a new diagnosis based on the latest guidelines [22,23]. All patients underwent a systematic assessment for substance use, and clinical and demographic data were collected through interviews and structured questionnaires, including age, sex, race, substance use

history, comorbidities, WHO functional class, and medications. The diagnosis of methamphetamine-induced PAH was based on history or a structured questionnaire confirming significant methamphetamine exposure. Patients with methamphetamine-induced PAH had a negative history and no other causes of pulmonary hypertension were identified. The earliest recorded diagnosis in the cohort was June 10, 2002. The mean follow-up from diagnosis was 54.8 months (SD = 35.2 months). To estimate 5-year survival, follow-up periods greater than 5 years were capped at 60 months, resulting in a mean follow-up of 44.5 months (SD = 17.3 months). Mortality data were collected through 2023 through analysis of medical records, publicly available obituaries, or social media [20].

Hemodynamic data

Hemodynamic data were obtained from the initial right heart catheterization performed at or shortly after diagnosis, including pulmonary artery systolic pressure, pulmonary artery diastolic pressure, mean pulmonary artery pressure, and cardiac index measured by the Fick method. Pulmonary vascular resistance (PVR) was calculated as (mean pulmonary artery pressure – right atrial pressure [RAP])/cardiac output. Right ventricular performance index (RVSWI) was calculated as (stroke volume/body surface area) × (mean pulmonary artery pressure – right atrial pressure [RAP]) × 0.0136 [24,25]. The pulmonary artery pulsatility index (PAPI) was calculated as (pulmonary artery systolic pressure – pulmonary artery diastolic pressure)/RAP [26].

Deformation analysis

Two-dimensional images for strain analysis were acquired at a frame rate of 50–90 Hz. Right ventricular (RV) free wall strain and right atrial (RA) reservoir strain were analyzed by two trained physicians (EO and DYL) using TomTec Arena, TTA 2.41 (TomTec, Unterschleißheim, Germany). RV free wall strain was analyzed from the RV apical four-chamber image focusing on the RV using the AutoStrain RV package, and RA reservoir strain was obtained from the RA apical four-chamber image focusing on the RA using the AutoStrain left atrial (LA) package. RA strain was calculated using the onset of the QRS wave (end of atrial systole) as the zero reference point, with the overall magnitude of the strain curve corresponding to the reservoir strain. Due to concomitant arrhythmia, only reservoir strain was analyzed in some patients participating in the study. While right atrial reservoir strain is typically reported as a positive value and right ventricular free wall strain as a negative value, in this study, strain values were presented as absolute values to simplify interpretation. Several limitations of this analysis should be noted. Right atrial (RA) deformation analysis was performed using a TomTec software package specific to the left atrium (LA), as such a package is currently unavailable. This issue was addressed by selecting an RA-focused view from the 4-chamber imaging window, allowing the software to track parameters similarly to the left atrium. Despite using an RA-focused view, manual adjustments were required to achieve optimal tracking, creating the potential for human error. Furthermore, the sample size and follow-up data on mortality and functional assessments were limited. The study was conducted at a single center and was retrospective [20].

Conclusion

In this study, conducted in two patient groups comparable in terms of mean pulmonary artery pressure, we demonstrated that methamphetamine-associated pulmonary arterial hypertension (MA-PAH) is characterized by more pronounced impairment of right heart deformation properties compared to idiopathic PAH (I-PAH). Despite similar right ventricular afterload, patients with MA-PAH had significantly lower right atrial reservoir strain and right ventricular free wall strain values, indicating more profound subclinical right myocardial dysfunction in this form of the disease. These data suggest that methamphetamine exerts a direct cardiotoxic effect, independently impairing right atrial and ventricular contractility and compliance, which is not explained solely by hemodynamic pressure overload. The identified differences in strain indices may provide key insights into the mechanisms underlying the more severe functional class, higher hospitalization rates, and reduced 5-year survival observed in patients with MA-PAH compared to I-PAH in clinical registries. Thus, incorporating right atrial and right ventricular strain assessment into the echocardiographic examination protocol for patients with MA-PAH may improve the early detection of subclinical myocardial dysfunction, optimize risk stratification, and facilitate more aggressive management of this vulnerable patient population. Given the retrospective design, the use of left atrial software for right atrial analysis, and the limited sample size, these findings require confirmation in larger, prospective, multicenter studies with a unified approach to right heart strain analysis and longer follow-up periods. However, the presented results are the first to directly link impaired right heart straightness parameters with an unfavorable prognosis in MA-LAH, opening a new direction for pathophysiological and clinical research in this area.

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