# Regional Variation in Methamphetamine-associated Pulmonary Arterial Hypertension: Who'd Better Call Saul?

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Amphetamine use is prevalent, both worldwide and in the United States; it is estimated that approximately 27 million people, or 0.5% of the global adult population, as well as 2.3% of Americans between 15 and 64 reported amphetamine use (amphetamine, methamphetamine, or pharmaceutical stimulants) in the past year (1). Another study estimated that between 2015 and 2018, 6.6 adults per 1,000 had used methamphetamines. This same study found that individuals who used methamphetamines were more likely to be younger men with lower educational attainment, lower annual household income, and higher rates of co-occurring substance use as well as mental illness (2).

Within the United States, it has been commonly accepted that methamphetamine use varies significantly by region, with higher rates of use in the West and Midwest (3–5). Potential explanations for this difference range from differences in drug manufacturing and distributing, with more direct drug trafficking through Mexico through the western half of the country, to higher rates of depression, suicide, and concomitant drug use at higher elevations (1, 3, 4, 6).

The development of pulmonary arterial hypertension (PAH) was tied to stimulant use as early as the 1960s. Within 2 years of the introduction of aminorex fumarate, a novel weight-loss medication, rates of patients developing PAH significantly increased (7). Case reports began to surface in the 1990s of truck drivers who had previously used methamphetamines developing PAH (8). It was not until the early 2000s when methamphetamine use and the development of PAH were linked (9), and currently, methamphetamine is listed as a definite risk factor for PAH by the World Health Organization (WHO) (10).

The exact mechanisms of methamphetamine-associated PAH (Meth-APAH) are still unknown. Previous studies have shown that methamphetamine uptake is highest within the lungs, possibly contributing to direct pulmonary toxicity and vascular damage (11). Other studies have attributed damage to similarities between methamphetamines and serotonin, as serotonin may promote pulmonary smooth muscle cell proliferation and vascular remodeling or even induce DNA damage and impair the oxidative stress response (12, 13). Clinically, there have been few studies specifically evaluating patients with Meth-APAH. The largest was completed by a group from Stanford, which showed that when compared with patients with idiopathic PAH (IPAH), patients with Meth-APAH had more advanced heart failure symptoms, more severe hemodynamic abnormalities, and over twice the rate of clinical deterioration or death (14).

In this issue of *AnnalsATS*, Koliatis and colleagues (pp. 613–622) expand on these previous findings at a national level (15). Data was acquired from the Pulmonary Hypertension Association Registry (PHAR), a multicenter registry within the United States that follows patients establishing care at a Pulmonary Hypertension Care Center, where patients complete a tablet-based survey approximately every 6 months. The survey included information about socioeconomic status, social history, symptoms, current PAH therapies, heath-related quality of life (HRQL), and clinical outcomes, with baseline right heart catheterization hemodynamics included at the time of enrollment and 6-minute walk distance at baseline and each repeat clinical visit. The diagnosis and etiology of pulmonary hypertension was determined by the PHAR enrolling center; diagnosing physicians did not see survey results related to previous methamphetamine use. Analysis was restricted to patients with PAH either from amphetamine or methamphetamine use, using IPAH as a comparator group.

In total, of the 541 participants included, 118 (22%) had Meth-APAH, a total of 9% of the entire PHAR cohort. The authors found that participants with Meth-APAH were younger and less likely to be insured, college graduates, married, or employed, with lower taxable incomes compared with IPAH participants. Both groups were composed primarily of white females, but there was a higher percentage of men with Meth-APAH than IPAH. Participants in the Meth-APAH group had a greater 6-minute walk distance at baseline, but there was no significant difference in WHO functional class between groups. Notably, they found that 83% of all Meth-APAH participants were receiving care at PHAR centers in the Western U.S. Census Region.



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Participants with Meth-APAH had less favorable hemodynamics, including a higher right atrial pressure, lower cardiac output/cardiac index, and a lower right ventricular stroke volume index than participants with IPAH but no significant change in mean pulmonary artery pressure or pulmonary vascular resistance. Moreover, participants with Meth-APAH had more advanced WHO functional class despite no significant difference in a fully adjusted model of 6-minute walk distance. In an age- and demographic-adjusted model, participants with Meth-APAH had poorer generic-mental HRQL and PAH-specific HRQL, which was consistent over multiple visits. Furthermore, participants with Meth-APAH were less likely to receive triple therapy, parenteral therapy, or supplemental oxygen, but this group was more likely to be seen in the emergency department or hospitalized than participants with IPAH. Survival rates were similar between both groups, with no difference in lung transplantation referral rates. Given the lack of consensus on how much methamphetamine use is required for a participant to be diagnosed with Meth-APAH, the authors also performed five different sensitivity analyses on functional status, HRQL, treatment, and healthcare utilization models. These analyses did not substantially change the original findings.

There are a number of limitations to this retrospective study. All methamphetamine use was self-reported, use was only asked at the initial visit, and there were no laboratory studies to confirm or refute use. As previously mentioned, there is no consensus definition of how much methamphetamine use is required for the diagnosis of Meth-APAH, and it is impossible to know if ongoing use was occurring among participants. The survey used did not report duration of symptoms prior to presentation, thus the worsening hemodynamics seen among this group may be the result of delayed time to presentation versus a more aggressive phenotype. The PHAR requires opting into the registry, so selection bias is also possible.

Despite these limitations, this study is the first of its kind to report the frequency of Meth-APAH on a national scale. There are a number of follow-up questions that arise from the results: is there truly a difference in mortality in this subset of patients, as previously found (14)? Given the fact that amphetamine use seems to be rising on a national and global scale (1, 3), how will these findings evolve over time? How do we explain the more severe hemodynamic findings seen in patients with Meth-APAH? What role does a possible coexisting methamphetamine-associated cardiomyopathy play with possible uncoupling of the right ventricle (16, 17)? Are there associated environmental, genetic, or epigenetic predisposing factors to Meth-APAH? More importantly, however, these results reflect and highlight the societal impact of our national public health crisis associated with economic disenfranchising, mental illness, and disparities in access to appropriate and comprehensive health care.

In summary, despite significant limitations, the study by Koliatis and colleagues brings forth additional evidence of the impact of Meth-APAH and substantiates the need for further studies investigating the pathobiology, treatment, and prevention of this devastating complication of methamphetamine abuse. While searching for the answers to these questions, we should heed the findings of this study to inform our care and research of patients with Meth-APAH. In the words of Jimmy McGill, "Perfection is the enemy of perfectly adequate." ■

**Author disclosures** are available with the text of this article at www.atsjournals.org.

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