# Letters

## Cases of Phenotypic Switching From Dilated Cardiomyopathy to Pulmonary Arterial Hypertension in Chronic Methamphetamine Users

Methamphetamine-associated cardiomyopathy (MA-CMP) and methamphetamine-associated pulmonary arterial hypertension (MA-PAH) are considered distinct cardiovascular sequelae of chronic methamphetamine (MA) use.

We report 14 patients, all with initial diagnoses of classic dilated biventricular failure pattern of MA-CMP, who subsequently switched to MA-PAH/right ventricular failure phenotype. This novel clinical observation highlights the genetic susceptibility and mechanistic interplay between these 2 entities. Though rare, patients who have gone through both MA-CMP and MA-PAH phases may experience high mortality with barriers to receiving standard treatments.

With the consistent uptrend of MA use worldwide, MA-associated cardiovascular sequelae have attracted increasing attention from clinicians, public health domains, as well as the general public.[1] We have previously compared 2 major cardiac disease phenotypes associated with MA use, dilated cardiomyopathy (CMP) (MA-CMP) and pulmonary arterial hypertension (PAH) (MA-PAH),[2] which have been considered distinct entities with unique pathophysiology, clinical course, and treatment strategies. While both carries high mortality, up to one-third of patients with MA-CMP were observed to have normalized their left ventricular (LV) function if cessation of MA use and heart failure (HF) specific therapies were implemented early when the right heart was not yet involved.[3] In this brief report, we describe a series of 14 patients, all with initial diagnosis of MA-CMP, who subsequently normalized LV systolic function and developed MA-PAH with severe pulmonary arterial hypertension and predominant right ventricular (RV)

failure (Table 1). The Institutional Review Board of Santa Clara Valley Medical Center approved the study protocol.

The case series included 5 women and 9 men, predominantly White (n = 9), with age ranging from 22 to 61 years (median 50 years, IQR: 17 years) at time of MA-CMP diagnosis. The median left ventricular ejection fraction was 30% (IQR: 10%). The median time interval between switching from MA-CMP to MA-PAH was 1.5 years (IQR: 2.8 years). Right ventricular systolic pressure (RVSP) was 52 mm Hg [IQR: 15 mm Hg] during MA-CMP, and was further increased to 68 mm Hg (IQR: 20 mm Hg) after switch to MA-PAH, while left ventricular ejection fraction normalized to 55% (IQR: 5%). Two notable echocardiographic features of this cohort were: 1) normal left heart volumes (left ventricular end diastolic volume index = 43 [IQR: 14] mL/m$^2$, left ventricular end-systolic volume index = 20 [IQR: 8] mL/m$^2$, and left atrial volume index = 24 [IQR: 11] mL/m$^2$) despite severely reduced LV systolic function; and 2) significant RV impairment (increased RV dimension, decreased right ventricular fractional area change, and 10 patients with ≥ moderate functional tricuspid regurgitation) during the MA-CMP phase. Three patients (2, 4, and 14) had echocardiograms in between MA-CMP and MA-PAH phases showing normalized biventricular function prior to the switch.

Clinically, 4 patients had history of intracardiac thrombi, including patient 13 with both LV thrombi and RV thrombi. All carried diagnosis of hypertension. Six of 14 patients (43%) were smokers and 6 of 14 (43%) abused alcohol. Confirmatory right heart catheterization was completed in 4 patients, patients 1, 5, 7, and 11, during MA-PAH phase of the disease. Four patients received PAH therapy (patient 5 on ambrisentan/sildenafil; patient 6 on bosentan/sildenafil/oral treprostinil; both patients 7 and 11 were on sildenafil only). Four patients had documented cessation from MA use. There were 6 deaths in this cohort with age at death ranging from 31 to 70 years old over a median of 52 months follow-up. It is worth noting that all the patient who died (n = 6) were not on PAH therapy and all patients who stopped using MA lived (n = 4). Selection bias such as poor compliance, poor social support, worse comorbidities, and more severe PAH/HF symptoms may

**TABLE 1  Clinical and Echocardiographic Characteristics of Case Patients**

| | | | | | | | Patient # | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| Sex | M | F | M | M | F | F | M | F | M | M | M | F | M | M |
| Race/ethnicity | White | White | White | Black | White | Asian | White | White | Hispanic | White | White | Hispanic | White | Hispanic |
| Age at MA-CMP (y) | 45 | 37 | 51 | 22 | 56 | 29 | 34 | 50 | 40 | 61 | 58 | 56 | 52 | 54 |
| Age at MA-PAH (y) | 47 | 41 | 51 | 31 | 57 | 37 | 36 | 50 | 43 | 70 | 59 | 57 | 53 | 55 |
| Death (age, y) | Yes (56) | Yes (41) | Yes (51) | Yes (31) | – | – | – | Yes (52) | – | Yes (70) | – | – | – | – |
| Follow-up (mo) | 130 | 45 | 3 | 96 | 86 | 121 | 53 | 27 | 34 | 102 | 51 | 30 | 41 | 55 |
| PAH therapy | No | No | No | No | Yes | Yes | Yes | No | No | No | Yes | No | No | No |
| HF therapy | Carvedilol/ lisinopril | No | No | No | No | Carvedilol/ spironolactone | Spironolactone | Losartan/ carvedilol | Carvedilol/ spironolactone | No | Carvedilol | Losartan/ metoprolol succinate | No | Carvedilol/ lisinopril |
| Cessation of MA | No | No | No | No | Yes | Yes | No | No | No | No | Yes | No | Yes | No |
| Initial LVEF (%) | 30 | 26 | 36 | 22 | 34 | 20 | 31 | 35 | 40 | 37 | 25 | 30 | 30 | 25 |
| RVFAC (%) | 13 | 13 | 22 | – | 12 | – | 15 | – | 14 | 37 | – | 23 | 25 | – |
| Mid-RV dimension (cm) | 3.6 | 3.8 | 4.6 | – | 5.4 | – | 5.0 | – | 4.4 | 3.7 | – | 4.4 | 4.6 | – |
| RVSP (mm Hg) | 36 | 65 | 57 | 28 | 54 | 55 | 57 | 61 | 46 | 26 | 40 | 48 | 49 | 56 |
| Postswitching LVEF (%) | 54 | 50 | 55 | 55 | 58 | 50 | 55 | 60 | 50 | 61 | 55 | 57 | 51 | 53 |
| RVFAC (%) | 12 | 17 | 12 | 25 | 25 | 15 | 17 | 16 | 12 | – | 12 | 4.5 | 13 | 14 |
| Mid-RV dimension (cm) | 4.5 | 3.4 | 6.5 | 3.6 | 4.0 | 5.8 | 5.9 | 3.8 | 6.5 | – | 5.9 | 16 | 5.6 | 3.3 |
| RVSP (mm Hg) | 74 | 54 | 80 | 60 | 71 | 90 | 63 | 90 | 57 | 84 | 54 | 58 | 68 | 68 |

HF = heart failure; LVEF = left ventricular systolic function; MA = methamphetamine; MA-CMP = methamphetamine-associated cardiomyopathy; MA-PAH = methamphetamine-associated pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; RV = right ventricle; RVFAC = right ventricular fractional area change; RVSP = right ventricular systolic pressure.

preclude initiation of PAH therapy in those who died without being treated. The role of MA cessation and PAH specific therapy in patients exhibiting this rare condition deserves further investigation.

As far as we know, this is the first report of phenotypic switching from MA-CMP to MA-PAH, a phenomenon that has not been previously observed in MA-associated or other types of dilated CMP. Unlike the historical cohort of 107 reversible MA-CMP reported previously by our group,[3] patients underwent phenotypic switch between MA-CMP and MA-PAH had normal LV chamber sizes and more severe right heart dilatation/dysfunction/functional tricuspid regurgitation at baseline (**Table 1**). Though it is possible that this switching phenomenon is a subtype of reversible MA-CMP with normalized LV but persistent RV dysfunction, the following observations argue against this hypothesis: 1) 3 patients in this cohort coincidentally had echocardiograms in between MA-CMP phase and MA-PAH phase, with normalized LV as well as RV size and function; 2) these 14 patients had normal left heart chamber sizes, but worse RV dilatation/systolic dysfunction/higher RVSP at baseline than the historical reversible MA-CMP group.[3] This finding is contrary to our experience with

MA-CMP where RV involvement occurs late during the natural history after the LV is significantly dilated; and 3) after switching from MA-CMP to MA-PAH, RVSP increased further (from a median of 56 to 68 mm Hg). If the right HF is mainly due to LV failure, RV dilation and RVSP are expected to improve after normalization of LV, which is opposite of what is observed in this cohort. Therefore, we favor the underling pathophysiology for the phenotypic switch to be de novo development of MA-PAH upon fully normalized biventricular function in genetically susceptible individuals.[4]

Currently, no studies have evaluated specific therapies to treat MA-CMP or MA-PAH. Cessation from MA use remains the cornerstone of clinical management, in addition to standard medical regimens for non-ischemic dilated CMP and idiopathic PAH, respectively. Due to the frequent coexistence of psychiatric diseases, limited social support particularly homelessness, and the highly addictive nature of MA, many patients with MA-CMP and MA-PAH lack the insight and/or support system to access medical care.[1] This is reflected in our cohort of 14 patients, with 6 deaths over just more than 4 years (median) of follow-up. Cardiac catheterization and disease specific medical

therapies were only implemented in a small fraction of the cohort as well. With the publication of this small series, we hope to draw attention to this rare phenomenon. Be it de novo development of group 1 PAH after resolution of dilated CMP (the phenotypic switch hypothesis), vs persistent World Health Organization group 2 pulmonary hypertension after resolution of LV dysfunction (the partial reversal hypothesis), the uniqueness of this phenotype calls for vigilance and recognition from other institutions or registries where MA-associated cardiac diseases are frequently encountered. More in-depth analyses of imaging data, genetic testing, and examination of autopsy specimens will provide valuable insights into its pathophysiology.

This case series derived from clinical encounters and not from an exhaustive chart review of all patients with MA-CMP. Therefore, the prevalence and incidence of this phenomenon cannot be established. Secondly, the number of cases is small so no statistical analysis performed. For example, the racial/ethnic makeup of the group likely reflects the demographics of the area with its usual clientele and should not be construed as showing that certain racial/ethnic groups (such as Blacks and Asians) are less likely to exhibit this sequence of events. Lastly, we welcome other centers with high volume MA-CMP cases to share their experience with regard to MA-CMP to MA-PAH phenotypic switching.

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