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Research Article

The Clinical, Electrocardiographic and Echocardiographic Profile of Adult Filipino Patients with Methamphetamine Induced Cardiomyopathy at the UP Philippine General Hospital

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Abstract

Background: Methamphetamine (MAP) abuse is not only a rampant sociopolitical issue plaguing our society today. It is an emerging and evolving medical problem since MAP use is an established cause of cardiac toxicity causing cardiomyopathy, arrhythmias, vasculitis, early onset atherosclerosis and myocardial infarction. While the incidence of MAP-related cardiovascular events (MAP CVE) is not established locally, Filipino cardiologists are seeing an increasing number of these patients at our clinics. Presently, review of local literature showed dearth of information on the clinical profile, diagnostic work up and outcomes of Filipino patients with MAP CVE and this research aims to fill this identified information gap.

Objectives: To describe the clinical, electrocardiographic, echocardiographic profile and in-patient clinical outcomes of adult patients admitted at the UP PGH from January to October 2016 with a clinical diagnosis of methamphetamine induced cardiomyopathy (MAP CM).

Methods: This is a prospective descriptive study on adult patients admitted at the UP PGH emergency room with a clinical diagnosis of MAP induced cardiomyopathy presenting with symptoms and signs of Heart Failure (HF) based on the New York Heart Association Functional Classification (NYHA FC) with a documented positive urine MAP test and/or use of MAP based on history. Patients with known cardiac or systemic comorbidities known to cause cardiomyopathy have been excluded. Convenient sampling method (total enumeration) was employed in the study. Descriptive statistics were reported.

Results: Twenty-two patients were enrolled. The most common complaints prompting ER consult were dyspnea (77%) and paroxysmal nocturnal dyspnea (68%). All patients were males and less than 60 years old (95%). Majority (73%) had low educational attainment and 41% were unemployed. Four in 10 patients were MAP users for more than a decade, 77% were smokers (mean of 18 pack years), 82% were alcoholic drinkers and 5% had concomitant cocaine abuse. Hypertension (36%), ischemic stroke (9%) and ACS (9%) were the common comorbidities identified. Three in 10 patients had a previous hospitalization for HF with an average of 1 - 2 admissions per year. About 35% were urine MAP positive on admission and 77% were admitted for acute HF or acute decompensation of HF. Six of 10 patients were in NYHA FC II-III and 30% were in cardiogenic shock. The mean duration of HF symptoms is 1.3 months and less than 25% of patients were receiving guideline directed medical therapy for HF on admission.

ECG profiling showed 82% had sinus rhythm, 14% had atrial fibrillation and 5% had complete heart block. About 40% were tachycardic on admission, 14% had wide complex QRS, 55% had left ventricular hypertrophy, 45% had left atrial abnormality, 41% had low voltage complexes, 36% had evidence of a previous infarction, 18% had acute ST elevation myocardial infarction, 27% had evidence of ischemia and 23% had fragmented QRS. Echocardiographic data revealed left ventricular dilatation (73%), right ventricular dilation (36%), left atrial dilation (45%, mean LAVI 4.7 cm2), diastolic dysfunction (27%) with reduced ejection fraction (60%, mean EF: 29% by Teicholz and 13% by Simpsons). Thirty percent had coronary angiogram with 57% having significant CAD. The mean duration of hospitalization is 9 days during which 18% had cardiogenic shock, 9% had ACS, 9% had nosocomial infection and 5% had bleeding complications. Majority (95%) was discharged improved with 86% on NYHA FC I-II. One patient died due to ventricular fibrillation.

Conclusion: To our knowledge, this is the first prospective study detailing the clinical, electrocardiographic and echocardiographic features as well as in patient outcomes of adult Filipino patients with MAP CM that can guide Filipino cardiologists/internists in the early recognition and prompt management of this escalating sociopolitical and clinical concern.

Keywords: Methamphetamine (MAP); MAP-Related Cardiovascular Events (MAP CVE); Methamphetamine Induced Cardiomyopathy (MAP CM)

Introduction

Epidemiology/Burden of disease

The escalating number of methamphetamine (MAP) users worldwide is estimated to be about 26 million, mostly aged 15-64 years old, almost two-thirds of which reside in East and South-East Asian countries [1]. The Philippines ranked as the country with the highest abuse rate for MAP or "shabu" in East Asia, according to the latest United Nations World Drug Report [1]. Data from the National Bureau of Investigation in 2012 states that 2.1 % of Filipinos aged 16 to 64 were using MAP and domestic consumption of MAP and marijuana continues to be the main drug threats in the country [2]. In the Philippines, as in neighboring Asian countries, methamphetamine is the drug of choice of over 90% of Filipino drug users [3].

Methamphetamine is a highly addictive psychostimulant drug, chemically related to amphetamine, which produces euphoria and stimulant effects. Since it is easily manufactured from inexpensive and readily obtainable chemicals, its availability led to the widespread and rampant abuse of this dangerous and prohibitive drug. Compared to other countries, methamphetamine is cheaper In the Philippines, a single "pingi" or 0.1 gm costs only P100 while one mongo-sized "gram" costs P1,000 - 2,000 in contrast to 1997 methamphetamine prices in the U.S. ranging from $3,500 to $30,000 per pound, $400 to $2,800 per ounce, and $37 per gram in the Seattle area to $300 per gram in the New York area [3]. In fact, a mandatory "surprise" testing in one precinct in the Philippines found 69% positive for drug use [3].

Review of Related Literature

Methamphetamines exert its sympathomimetic effects by stimulating the central nervous system through excessive release of excitatory neurotransmitters such as norepinephrine, epinephrine, dopamine and serotonin while simultaneously blocking the reuptake at the sympathetic synaptic receptors which eventually leads to several clinical effects such as inducing euphoria, intensifying emotions, altering self-esteem, and increasing alertness, aggression, and sexual appetite [4,10,12]. Both acute and chronic MAP abuse lead to significant cardiovascular sequelae. Acute methamphetamine overdose can lead to rhabdomyolysis, sympathetic overdrive, cardiovascular collapse, ventricular tachyarrhythmia, and even death [5]. On the other hand, cardiologists have contended that chronic MAP abuse produces a myriad of chronic cardiac toxic effects. MAP and cocaine abuse has been established causes of cardiac toxicity leading to cardiomyopathy, increased susceptibility to malignant arrhythmias, vasculitis, early onset atherosclerosis, pulmonary edema, myocardial infarction and aortic dissection independent of the route of administration [6]. In 2007, Yeo reported that methamphetamine use is present in at least 5% of all patients presenting at the emergency room with heart failure and 40% of patients under the age of 45 admitted to the hospital with cardiomyopathy [7] highlighting its crucial role as an etiology of heart failure in young individuals.

Numerous references acknowledged the likelihood of cardiomyopathic changes with methamphetamine use, but generally as one among many varied cardiovascular effects and injuries [7]. The existence of human methamphetamine cardiomyopathy may be inferred from case reports but the association is not conclusive 8,9,10. Newton *et.al*. described both cardiovascular and subjective effects of cocaine and methamphetamine and noted that the persistent tachycardic and hypertensive effects of methamphetamine, extending well beyond those of cocaine, could not be explained on the basis of pharmacokinetics alone. They postulated central nervous system mediation for these effects [11]. The cellular basis for MAP cardiomyopathy is postulated to be due to the myocyte hypertrophy and fibrosis [8,9]. Pre-clinical studies done on animal exposed to methamphetamine for 12 weeks showed cellular changes such as atrophy, hypertrophy, patchy cellular infiltration and fibrosis. Interestingly, with the cessation of MAP exposure, gradual recovery of myocytes was observed starting 3 weeks after discontinuation of exposure [9]. Rajs described the pathologic findings of cardiac chamber enlargement, left ventricular hypertrophy, hemorrhage, fibrosis and contraction-band necrosis in 14 subjects who previously used MAP [13].

Clinical experience with MAP users suggested a higher incidence of electrocardiographic abnormalities. Goebert in 2007 showed that significant variance from the normal population was noted in the electrocardiograms of the study cohort. Among the ECG abnormalities noted was a prolongation of the corrected QT (QTc) interval beyond 440 ms in 27.2% of the group. QTc prolongation to this extent poses a particular risk for ventricular arrhythmias, most notably Torsades de Pointes [12].

In a study published in 2003, 84% of patients with MAP use underwent echocardiography with consistent findings of dilated cardiomyopathy and global ventricular dysfunction to varying degrees in most patients6. Similarly, Ito., *et al* in 2009 looked retrospectively at young patients (age < 45 years) who were admitted for cardiomyopathy or heart failure. After exclusion of coronary artery disease or valvular heart disease, patients were divided into 2 groups, one that used methamphetamine and another that did not. The group that used methamphetamine had higher left ventricular volumes and lower left ventricular ejection fraction than non users on echocardiography [14].

In terms of clinical outcomes, isolated case reports suggest that methamphetamine associated cardiomyopathy is reversible with discontinuation of abuse [11].

Implication and importance

Although the actual incidence of MAP related cardiovascular event is not well established in local literature, Filipino cardiolo-

gists are seeing an increasing number of these patients at our clinics. At present, review of locally published literature showed scarcity of information on the clinical profile, electrocardiographic and echocardiographic features as well as in patient outcomes of adult Filipino patients with methamphetamine induced cardiomyopathy that can guide Filipino cardiologists in early diagnosis and management of this clinical condition.

Research question

What are the clinical profile, electrocardiographic and echocardiographic features and in patient outcomes of adult Filipino patients admitted at the emergency room, wards and medical intensive care unit of Philippine General Hospital from May 2016 to October 2016 with a clinical diagnosis of methamphetamine induced cardiomyopathy.

Objectives

General objectives

To describe the clinical, electrocardiographic and echocardiographic profile of adult Filipino patients admitted at the emergency room, medicine wards, and medical intensive care unit of the University of the Philippines, Philippine General Hospital (UP-PGH) from May 2016 to October 2016 with a clinical diagnosis of methamphetamine induced cardiomyopathy.

Specific objectives

1. To determine the prevalence of methamphetamine induced cardiomyopathy among admitted adult patients in PGH.
2. To describe the clinical profile and cardiac manifestations of patients with a history of methamphetamine use and/ or biochemical evidence of methamphetamine seen at the UP-PGH.
3. To describe the electrocardiographic profile of patients with a history of methamphetamine use and/ or biochemical evidence of methamphetamine seen at the UP-PGH.
4. To describe the echocardiographic profile of patients with a history of methamphetamine use and/or biochemical evidence of methamphetamine seen at the UP-PGH.
5. To describe the laboratory profile of patients with a history of methamphetamine use and/or biochemical evidence of methamphetamine seen at the UP-PGH.
6. To describe the in patient course, in patient management and in patient mortality rates of patients with a history of methamphetamine use and/ or biochemical evidence of methamphetamine seen at the UP-PGH.

Methodology

Setting

This research endeavor will be a retrospective study to be conducted at the University of the Philippines – Philippine General Hospital (UP-PGH), a tertiary medical center.

Study population

All adult patients (19 years old and above) admitted at the emergency room, wards and intensive care unit of the UP-PGH with an initial clinical diagnosis of methamphetamine induced cardiomyopathy from May 2016 to October 2016 and who have not satisfied the exclusion criteria will be included in the study.

Inclusion criteria

Patients aged 19 years and older with symptoms and signs of heart failure based on the New York Heart Classification with

- Documented positive urine MAP test and/or
- Use of MAP based on clinical history.

Exclusion criteria

- 18 years old and below.
- Pregnant patients.
- Patients with the following co-existing diseases/conditions:
  - Primary valvular heart disease
  - Congenital heart disease
  - Autoimmune connective tissue diseases (SLE, Sarcoidosis)
  - Thyrotoxic Heart Disease
  - Chronic Kidney Disease
  - Familial Hypercholesterolemia
  - Infectious Cardiomyopathy (Bacterial, Viral, Parasitic)
  - Hemochromatosis
  - Chemotherapy induced cardiomyopathy
  - Genetic cardiomyopathies
  - Peripartal cardiomyopathy.

Study design: Retrospective Study Design.

Overview of methods:

- All adult patients admitted at the emergency room, wards and medical intensive care unit of the UP-PGH with a history of MAP use and/or laboratory evidence of methamphetamine with an admitting impression of methamphetamine cardiomyopathy will be assessed for inclusion. Communication will be made with the emergency room officers, physicians on duty and toxicology fellows/rotators at the start of the study to orient them on the study inclusion and exclusion criteria. Once assessed to be eligible for study inclusion, the chart will be reviewed for data collection.
- Data to be obtained from the chart will include demographic, clinical, electrocardiographic, echocardiographic and laboratory data using a standardized data collection form adapted from the Philippine Heart Association Heart Failure Registry Data Collection Form (See appendix A).
- The cardiovascular outcome data to be collected are:

- Duration of hospital stay.
- Cardiovascular mortality rate – defined as mortality from cardiac causes i.e. cardiac arrest, cardiac death.
- Causes of cardiovascular morbidity and mortality (i.e. acute coronary syndrome, cardiogenic shock, malignant arrhythmias, cerebrovascular accident, bleeding, acute respiratory failure, acute renal failure and nosocomial infection.
- New York Heart Association Functional Class on discharge.

Study duration: January 2016 -December 2016.

Sample size: Convenient Sampling Method.

Data management and analysis

Descriptive analysis will be carried out using tables, frequency, percentages, and mean values will be used to summarize the data collected. Descriptive analysis will be done by obtaining the mean and standard deviation of quantitative variables. For nominal data i.e. baseline characteristics or event rates of outcomes, absolute numbers and percentages will be utilized.

Ethical considerations

The study protocol will be submitted to University of the Philippines Manila Research Ethics Board (UPMRB) for ethical review and approval. The study will be conducted only upon approval from the UPMREB. All patient information will be anonymous and kept confidential. The data collection tool will be coded to keep the patient's information confidential. The data collected will be used solely for academic purposes. The research funding will come from the principal investigator. There will be no reimbursement to be made to the patient. There are no conflicts of interest identified for this research study.

Results

A total of 22 patients were identified and enrolled in this study. All of the patients enrolled were males and majority were young patients (95%). Majority (73%) of patients were able to reach secondary education while 46% were unemployed. About 8 in 10 patients were married or living with a common law partner. Majority (45%) of patients enrolled have been using MAP for >10 years. In terms of frequency of MAP use, the cohort has a bell shape distribution with majority (32%) of patients using MAP daily. For 18% of patients, it was their first time to use methamphetamine. About 5% of these patients had concomitant use of cocaine, 77% were smokers and 82% were alcoholic beverage drinkers. The most common comorbidity detected in the cohort was hypertension in 36%. About 3 in 10 patients had a previous history of hospitalization from heart failure and among those who were previously diagnosed with chronic heart failure, review of their medications showed inadequate guideline directed treatment.

About 86% presented with dyspnea while 14% presented with angina. Four in every 10 patients presented in NYHA FC IV and majority (73%) had acute decompensation of chronic heart failure. Three for every 10 patients tested positive on urine MAP test at the ER while 68% volunteered a history of MAP abuse yet were urine MAP negative on admission. The mean systolic blood pressure was 105.5 mmHg while the mean diastolic blood pressure was 66.5 mmHg. The average heart rate on admission was 95.2 beats per minute. Majority of patients (82%) had clinical signs of cardiomegaly, 45% had pedal edema, 37% had bilateral crackles and 41% had neck vein engorgement (see Table 1).

Demographic Profile	%
Sex	
Male	100%
Female	0%
Age	
19-60 years old	95%
> 60 years old	5%
Educational Attainment	
Elementary level	5%
Secondary level	73%
College level	18%
Employment Status	
Employed	54%
Unemployed	46%
Marital Status	
Married/Live in Partner	82%
Single	18%
Drug of Abuse	
Methamphetamine	100%
Cocaine	5%
Marijuana	0%
Years of MAP use	
Less than 1 year	14%
1-5 years	27%
5 -10 years	9%
> 10 years	45%
Frequency of MAP use	
Once only	18%
Daily	32%
Weekly	27%
Monthly	18%
Concomitant Substance Use	
Smoker	77%
Alcoholic Beverage Drinker	82%

Clinical Profile	%
Comorbidities	
Hypertension	36%
Diabetes	5%
Cerebrovascular Disease (Ischemic type)	9%
Chronic Stable Angina Pectoris	5%
Acute Coronary Syndrome	9%
Prior Hospitalization for Heart Failure	32%
Number of Hospitalization for Heart Failure	100%
1-2 x	
Prior Heart Failure Medications	
Ace Inhibitor / Angiotensin Receptor Blocker	23%
Beta-blockers	18%
Loop Diuretic	27%
Spironolactone	9%
Digitalis /Digoxin	9%
Calcium channel blocker	5%
Ivabradine	9%
Anti-platelet	14%
Anticoagulant	5%
Nitrates	9%
Statin	9%
Tolvaptan	5%
Presenting Symptom on Admission	
Dyspnea	86%
Chest pain	14%
NYHA Functional Classification	
I	0
II	32%
III	27%
IV	41%
Type of Heart Failure	
Acute Heart Failure	18%
Acute on top of Chronic Heart Failure	73%
Chronic Heart Failure	9%
Laboratory Evidence of Methamphetamine	
Urine MAP Positive	32%
Urine MAP Negative	68%
Blood Pressure on Admission	Mean
Systolic (in mmHg)	105.5
Diastolic (in mmHg)	66.5
Heart Rate (beats per minute)	Mean 95.2
Physical Examination Findings	
Neck vein engorgement	41%
Crackles	37%
Left ventricular hypertrophy	82%
Edema	45%

Table 1: The clinical profile of patients with MAP induced cardiomyopathy.

On evaluation of baseline electrocardiogram (see Table 2), 82% were in sinus rhythm while 13% were in chronic atrial fibrillation. One patient had 3rd degree AV block on presentation. Half of patients had normal heart rates on ECG, while 41% were tachycardic. About 14% had left axis deviation, 55% had left ventricular

Electrocardiographic Profile	Mean/%
Rhythm	
Sinus	82%
Atrial Fibrillation/Flutter	13%
AV Blocks (3rd Degree AV Block)	5%
Baseline Heart Rate	
Normal	50%
Sinus Tachycardia	41%
Sinus Bradycardia	9%
Axis	
Normal	86%
Left Axis Deviation	14%
QRS duration	
≤ 0.12 ms	86%
> 0.12 ms	14%
QTc interval	
< 430 ms	68%
> 430 ms, < 440 ms	9%
> 440 ms	23&
Chamber Enlargement	
Left ventricular hypertrophy	55%
Right ventricular hypertrophy	0
Left Atrial Abnormality	45%
Right Atrial Abnormality	23%
Poor R wave Progression	18%
Low Voltage QRS complex	41%
Old Infarction	36%
Ischemia	
STEMI	18%
ST segment depression	27%
Arrhythmias	
Supraventricular	
Premature atrial complex	0
Tachycardia	0
Ventricular	
Premature ventricular complex	9%
Tachycardia	0
Fibrillation	0
Right Bundle Branch Block	9%
Left Bundle Branch Block	0

Table 2: The electrocardiographic profile of patients with MAP induced cardiomyopathy.

hypertrophy, 45% had left atrial abnormality and 23% had right atrial abnormality. Majority had narrow complex QRS while 14% had wide complex QRS. About 23% presented with prolonged QT interval. Two for every 10 patients had poor R wave progression while 4 in every 10 patients had low voltage QRS complexes. Thirty six percent had ECG evidence of an old infarction. About 18% presented with ST elevation myocardial infarction while 27% had significant ST segment depression consistent with subendocardial ischemia. About 9% had documented premature ventricular complexes on ECG.

On echocardiographic evaluation, majority (81%) of the cohort had eccentric left ventricular hypertrophy, 36% had right ventricular dilatation, 45% had left atrial enlargement and 41% had right atrial enlargement. Left ventricular systolic function was depressed in 27% with a mean ejection fraction of 26.2% by Simpson's method. Rheologic stasis was present in 23% while left ventricular thrombus was documented in 5%. Majority (72%) had wall motion abnormality with 54% having global hypokinesia and 18% presented with segmental wall motion abnormality. Six in every 10 patients had evidence of diastolic dysfunction. Mitral regurgitation was the most common valvular defect identified. About 36% had evidence of varying degrees of pulmonary hypertension.

Echocardiographic Profile	%
Chamber Enlargement	
Left Ventricle	
Concentric remodeling	14%
Concentric hypertrophy	5%
Eccentric hypertrophy	81%
Right ventricle Dilatation	36%
Left Atrial Enlargement	45%
Right Atrial Enlargement	41%
Mean Left Atrial Volume Index (in ml/m^2)	46.88
Tricuspid Annular Plane Systolic Excursion (TAPSE)	14.18
Ejection Fraction (by Simpson's method)	
≥ 40%	27%
< 40%	59%
Mean Ejection Fraction (by Simpson's method)	26.2%
Left ventricular	
Thrombus formation	5%
Rheologic stasis	23%
Wall Motion Abnormality	72%
Segmental hypokinesia	18%
Global hypokiensia	54%
Diastolic Dysfunction	59%
Valvular Insufficiency	
Aortic Regurgitation	27%
Mitral Regurgitation	64%
Tricuspid Regurgitation	59%
Pulmonary Hypertension	
Mild	9%
Moderate	18%
Severe	9%

Table 3: The Echocardiographic Profile of Patients with MAP Induced Cardiomyopathy.

On the other hand, the review of laboratory data was presented in Table 4. Majority of patients had low serum magnesium (0.72 mmol/L), low corrected serum calcium (1.9 mmol/L) and low serum albumin (26 g/L) levels. Mean fasting blood sugar was elevated (134.5 mg/dL) while the mean HbA1C was 5.8% likely representing stress hyperglycemia among acutely ill MAP patients. The mean LDL cholesterol is 83.84 md/dL while the mean HDL cholesterol is low at 27 mg/dL. Among those who underwent coronary angiography (32%), 57% had angiographic findings of concomitant significant coronary artery disease while 43% had non significant atherosclerosis.

Laboratory Profile	Mean
Creatinine (in mmol/L)	108.90
Blood urea nitrogen (in mmol/L)	14.17
Sodium (in mmol/L)	136.22
Potassium (in mmol/L)	3.88
Calcium (in mmol/L)	1.90
Magnesium (in mmol/L)	0.72
Albumin (g/L)	26.04
Fasting blood sugar (in mg/dL)	134.5
HBA1C (in %)	5.8
Total Cholesterol (in mg/dL)	130
Low Density Lipoprotein (in mg/dL)	83.84
High Density Lipoprotein (in mg/dL)	27
Trigylceride (in mg/dL)	100
Creatinine Kinase Total (in ng/mL)	1869
Creatinine Kinase MB (in ng/dL)	139

Table 4: The Laboratory Profile of Patients with MAP Induced Cardiomyopathy.

On following up the cohort, majority of patient received guideline directed medical treatment for heart failure. Note that 77% received ACE inhibitor/ARB, 55% were on beta blockers, 50% were on loop diuretics, 50% on spironolactone and 45% were on digitalis. Due to concomitant coronary artery disease, 66% were on anti-platelets, 50% on anticoagulants, 55% on statins and 36% were on nitrate therapy. The mean duration of hospital stay is 9.14 days. Majority (95%) were discharged with improved NYHA functional class. Thirty two percent were in NYHA FC I, 55% in FC II and only 5% in FC III. During the course of hospitalization, 18% developed cardiogenic shock, 9% developed acute coronary syndrome and 1 patient developed ventricular fibrillation which led to sudden death. Other non-cardiac complications noted were nosocomial pneumonia in 9% and upper gastrointestinal bleeding in 5%.

In Hospital Course	Mean/%
Medications given while admitted	
Ace Inhibitor/Angiotension Receptor Blocker (ARB)	77%
Beta-blockers	55%
Loop Diuretic	50%
Spironolactone	50%
Digitalis	45%
Ivabradine	14%
Anti-arrhythmic Drugs (i.e. Amiodarone)	5%
Antiplatelet	66%
Anticoagulant	50%
Nitrates	36%
Fish Oil	18%
Statins	55%
Duration of Hospital Stay (in days)	Mean 9.14
Mortality rate	5%
In Patient Course	
Cardiogenic shock	18%
STEMI	9%
Ventricular fibrillation	5%
Hospital acquired pneumonia	9%
Gastrointestinal bleeding	5%
NYHA Functional Classification on Discharge	
I	32%
II	55%
III	5%

Table 5: The In-Patient Clinical Course of Patients with MAP Induced Cardiomyopathy.

Discussion

Epidemiology, Demographics and Clinical Profile

This research endeavor documented a total of 22 patients with documented MAP cardiomyopathy in 1 year in the largest tertiary hospital in the Philippines. Previously published data on the prevalence and incidence of MAP cardiomyopathy in the Philippines is not available, hence comparison is not feasible at this point. Looking at global trends, according to the 2011 National Survey on Drug Use and Health, illicit-drug use had risen to nearly its highest level in last 10 years in the United States, with 8.7% of Americans age ≥12 years, or approximately 22.5 million people, saying they had used illicit substances in the month prior to the survey [15]. Our Filipino data can be taken as the baseline information on the incidence of MAP cardiomyopathy to which future comparisons can be made.

Majority (95%) of our cohort were below 60 years old and 100% were males. This is consistent with international data that was reported by Wijetunga., *et al.* in 2003, the only case series of methamphetamine-related cardiomyopathy in present literature. Wijetunga., *et al*. who identified and described the characteristics of 21 crystal MAP users with cardiomyopathy showed that majority of these patients were also male (90%) and under 45 years of age (67%) [17]. In a Filipino case series by Parico in 2004, 8 cases were included and similarly, all subjects are male with a mean age of 33 ± 10.3 years and minimal cardiovascular risk factors [17]. Majority (73%) of patients were able to reach secondary education with even 18% reaching college level hence our cohort can be considered fairly educated. About 46% were unemployed which reflects that methamphetamine abuse despite its high costs is rampant among people with low socioeconomic background.

Majority (45%) of patients enrolled have been using MAP for >10 years. This is in contrast to the study by Parico [17] in which the average MAP use prior to developing cardiomyopathy was of 4.7 years. In terms of frequency of MAP abuse, our cohort has a bell shape distribution with majority (32%) of patients using MAP daily. However, for 18% of patients, it was their first time to use methamphetamine. While majority of patients reported in literature had a chronic history of MAP abuse, this finding highlights that the development of heart failure and its complications may not be dose or duration dependent. As reported by Kaye, the necessary and sufficient toxic dose to produce serious cardiovascular complications or death is unclear, as the response to a specific dose varies due to individual differences in responsiveness and variations in degree of tolerance [18]. The risk of complications may be higher with patterns of use that are associated with more frequent use and taking higher doses, such as injecting and smoking crystalline methamphetamine [18].

About 5% of these patients had concomitant use of cocaine, 77% were smokers and 82% were alcoholic beverage drinkers.

MAP cardiomyopathy may be confounded by polysubstance abuse, particularly alcohol and cocaine use. Mendelson., *et al.* showed that the concurrent administration of alcohol with methamphetamine increased the rate-pressure product as compared with methamphetamine use alone. This increase in cardiac workload may have a synergistic deleterious effect on the process of cardiomyopathy [19]. Fleury., *et al.* studied predictors of cardiovascular response such as increased heart rate and blood pressure to methamphetamine administration and recent alcohol use was found to be a predictor [20]. Previous research also suggests that the risk of cardiovascular problems among methamphetamine users is increased when the drug is combined with alcohol, cocaine or opiates [18]. The majority of regular methamphetamine users also smoke

tobacco, which is a known risk factor for heart disease. Therefore we cannot discount the possibility that tobacco is responsible for, or at least contributes to, some of the cardiac pathology found among methamphetamine users [18].

The most common comorbidity detected in the cohort was hypertension in 36%. Interestingly, a few patients were previously diagnosed with coronary artery disease. Literature review revealed that low level use of methamphetamine (sporadic, low dosage use) does not appear to be associated with major acute complications (i.e. myocardial infarction) or chronic cardiovascular disease, in an otherwise healthy user. 18 Methamphetamine may, however, exacerbate pre-existing underlying cardiac pathology, such as coronary atherosclerosis or cardiomyopathy, thereby increasing the risk of an acute event such as myocardial infarction or even sudden cardiac death [18]. Long-term methamphetamine users appear to be most at risk of cardiovascular damage, such as premature, accelerated coronary artery disease. As such, methamphetamine toxicity is more likely to have a fatal outcome with chronic use [18]. About 3 in 10 patients had a previous history of hospitalization from heart failure and among those who were previously diagnosed with chronic heart failure, review of their medications showed very inadequate guideline directed treatment. This reflects insufficient medical management for chronic heart failure among local doctors.

High catecholamine levels are known to be cardiotoxic, causing vasoconstriction, vasospasm, tachycardia, and hypertension [18]. In a retrospective study of the clinical features of methamphetamine toxicity, Lan., *et al.* (1998) found that, among emergency department patients presenting over a six year period, 89% were tachycardic and over half (56%) had hypertension. While tachycardia and hypertension are associated with increased demand for oxygen to the myocardium, vasoconstriction and vasospasm decrease the cardiac oxygen supply. The co-occurrence of these conditions induced by excess catecholamines affect the balance of cardiac oxygen supply and demand such that the overall effect is a reduction in the availability of oxygen to the heart [18]. In our cohort, the mean systolic blood pressure was 105.5 mmHg while the mean diastolic blood pressure was 66.5 mmHg while the average heart rate on admission was 95.2 beats per minute. None of our cohort fulfilled the criteria for acute MAP intoxication hence the absence of signs of adrenergic hyperstimulation. Majority of our patients (82%) had clinical signs of cardiomegaly, 45% had pedal edema, 37% had bilateral crackles and 41% had neck vein engorgement. This was consistent to the findings of Parico in 2004, that all Filipino MAP cardiomyopathy patients presented with symptoms and signs of congestive heart failure and radiographic findings of pulmonary congestion and cardiomegaly [17].

In our cohort, only 3 for every 10 patients tested positive on urine MAP test at the ER while 68% volunteered a history of MAP abuse yet were urine MAP negative on admission. Majority of our subjects involved were urine MAP negative. This is due to the fact that the half-life of the drug is approximately 9 to 12 hours, and this appears to be independent of the route of administration [16].

Electrocardiographic profile

Clinical experience with MAP abusers suggested a higher incidence of electrocardiographic abnormalities. A significant variance from the normal population was noted in the electrocardiograms of the study cohort. While 82% were in sinus rhythm, 13% were in chronic atrial fibrillation which can be correlated with left atrial abnormality on ECG and a dilated left atrium on echocardiography. One patient presented with 3rd degree AV block, which was not previously reported in older case series. This is probably related to the presence of concomitant ischemia to the SA or AV node or early degeneration of the sinus node. Chronic MAP exposure has been associated with decreased heart rate variability, impaired vagal function and reduction in heart rate complexity [22]. About 14% had left axis deviation, 55% had left ventricular hypertrophy, 45% had left atrial abnormality and 23% had right atrial abnormality consistent with the multi-chamber dilatation seen in the echocardiograms of patients with MAP cardiomyopathy. Twenty percent had poor R wave progression and 40% had low voltage QRS complexes, ECG findings consistent with cardiomyopathy. Thirty six percent had ECG evidence of an old infarction, 18% presented with ST elevation myocardial infarction and 27% had significant ST segment depression consistent with subendocardial ischemia. These findings strengthen the high correlation of accelerated atherosclerosis and coronary artery disease in MAP abusers. Interestingly, about 14% had wide complex QRS and 23% presented with prolonged QT interval. Among the ECG abnormalities that were previously noted in cohorts of MAP patients was a prolongation of the QTc beyond 440 ms seen in 27% of the cohort. QTc prolongation to this extent poses a particular risk for ventricular arrhythmias, most notably Torsades de Pointes [12]. In our cohort, one patient died of ventricular fibrillation which can be associated with these pro-arrhythmic ECG findings.

Echocardiographic profile

Wijetunga., *et al*. performed a retrospective analysis on patients discharged from a tertiary-care hospital with the diagnosis of MAP cardiomyopathy over a 4-year time period. Nineteen underwent echocardiography, which revealed dilated LV chamber size with globally depressed LV systolic function to varying degrees in most patients.23 In a Filipino case series by Parico in 2004, echocardiography of 8 patients revealed dilated left ventricle with global hypokinesia and low ejection fraction [17]. Similarly, on echocardiographic evaluation, majority (81%) of our cohort had eccentric left ventricular hypertrophy, 36% had right ventricular dilatation, 45% had left atrial enlargement and 41% had right atrial enlargement. Similarly, LV systolic function was depressed in 27% with a mean ejection fraction of 26.2% by Simpson's method. Majority (72%)

had wall motion abnormality with 54% having global hypokinesia and 18% presented with segmental wall motion abnormality. Unique to our cohort is the relatively high prevalence of rheologic stasis (23%) and left ventricular thrombus (5%), which can be correlated with the poor LV systolic function and low LV ejection fraction. These findings have potential management implications because routine anticoagulation is not yet recommended for MAP cardiomyopathy. Individualized oral anticoagulation may be considered for MAP cardiomyopathy patients with echocardiographic evidence of thrombus and/or rheologic stasis to prevent thromboembolic events.

In patient outcome profile

The mechanisms underlying the MAP cardiomyopathy observed in our cohort are most likely multifactorial. Proposed etiologies for cardiac injury include catecholamine excess, global coronary microvascular vasospasm and ischemia, increases in reactive oxygen species, mitochondrial injury, myoglobin loss, changes in myocardial metabolism and direct toxic effects [24,25]. Disruption of oxidative phosphorylation associated with myoglobin loss was proposed as a cause of cardiomyopathy with methamphetamine use [26]. In our cohort, majority of patient received guideline directed medical treatment for heart failure but of those who are eligible to received HF treatment, only 77% received ACE inhibitor/ARB, 55% were on beta blockers, 50% were on loop diuretics, 50% on spironolactone and 45% were on digitalis. This reflects the suboptimal management of heart failure in our subjects based from existing international and local guidelines.

The mean duration of hospital stay is 9.14 days and majority (95%) were discharged with improved NYHA functional class after prolonged hospitalization. While the implication on productivity loss on an individual patient basis is obvious, this finding has a potential public health implication in terms of increased government health insurance expenditure for such cases. This information can be used to approximate and project healthcare costs for future health policy purposes.

During the course of hospitalization, 18% developed cardiogenic shock, 9% developed acute coronary syndrome and 1 patient developed ventricular fibrillation which led to sudden death. It has been reported that vasospasm, accelerated atherosclerosis, acute coronary syndrome, sudden cardiac death, coronary, carotid and aortic dissections, arrhythmias and circulatory collapse are pathologies seen in MAP abuse [27]. In the study by Hong., *et al*, he described a patient with MAP abuse who succumbed to cardiogenic shock. Postmortem examination revealed diffuse transmural myocardial ischemia and focal areas of infarction. The coronary arteries, however, were free of obstructive lesions [28].

Other non-cardiac complications noted in our cohort were nosocomial pneumonia (9%) and upper gastrointestinal bleeding (5%). Like cocaine users, many MAP users present at the emergency rooms with respiratory symptoms [29]. Pulmonary hypertension was present in 36%, a finding that has been associated with pulmonary artery muscular hypertrophy with foreign body granulomas among MAP users [29]. Together with an immunocompromised state, this could have increased the risk for pulmonary infection. MAP abuse has also been associated with increased risk of developing giant gastrointestinal ulcers and ischemic colitis which could have been contributory to gastrointestinal bleeding on top of anti-platelet and anticoagulant therapy [29].

Conclusion

To our knowledge, this is the first prospective study detailing the clinical, electrocardiographic and echocardiographic features as well as in patient outcomes of adult Filipino patients with MAP CM that can guide Filipino cardiologists/internists in the early recognition and prompt management of this escalating sociopolitical and clinical concern.

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