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Exposure to Amphetamines Leads to Development of Amphetamine Type Stimulants Associated Cardiomyopathy (ATSAC)

Mahsa Jafari Giv[1]

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Abstract With rapidly rising prevalence of exposure to Amphetamine Type Stimulants (ATS), novel insights into cardiotoxic effects of this substance are being presented in the literature and remarkably ATS Associated Cardiomyopathy (ATSAC) is emerging as a novel cardiovascular condition with its distinctive pathogenesis, risk factors, clinical features and prognosis. A comprehensive systematic review was performed to explore and analyze the current evidence on the association between ATS exposure and development of cardiomyopathy, biological mechanisms involved in pathogenesis of ATSAC, risk factors, clinical features and course of patients with ATSAC. Several animal studies, case reports, case series and case-control studies support the association between ATS exposure and ATSAC. Oxidative stress, accelerated apoptosis, increased p53 activity, cardiomyocyte necrosis, perfusion defects, fatty acid toxicity, altered gene expression, abnormal cardiac protein synthesis and function in addition to defects in intracellular calcium hemostasis present themselves as likely mechanisms of cardiotoxicity in ATSAC. Majority of patients with ATSAC were found to be male, young and presented late with severe dilated cardiomyopathy. Female ATS users predominantly develop Takotsubo type of ATSAC and in particular its atypical basal variant. Overall, cessation of ATS exposure seems to be associated with some degree of reversibility and recovery in ATSAC sufferers.

✉ Mahsa Jafari Giv
Mahsa.JAFARIGIV@svha.org.au

[1] Department of Cardiology, St Vincent's Hospital (Melbourne), PO Box 2900, Fitzroy, VIC 3065, Australia

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Introduction

Detrimental effects of exposure to Amphetamine Type Stimulants (ATS) on cardiovascular system are being recognized at an alarming rate and reported in the literature. Whilst to date Amphetamine Type Stimulants Associated Cardiomyopathy (ATSAC) has not been precisely defined, nevertheless it is recognized as an acquired disease state characterized by otherwise unexplained cardiomyopathy in the setting of ATS exposure. ATS include mainly the substances amphetamine, methamphetamine and crystal methamphetamine, commonly referred to as "ice", and for this reason Methamphetamine-induced cardiomyopathy and Amphetamine-associated cardiomyopathy have also been interchangeably used in the literature to describe this cardiovascular disorder.

Amphetamine was first synthesized by the Romanian chemist Lazar Endeleanus in 1887 and later by Gordon Alles in 1927 [1]. In 1932, it was first marketed commercially as a nasal decongestant under the trade name Benzedrine™ by pharmaceutical company Smith, Kline and French [2]. In 1936 Benzedrine™ was sold in a 10 mg preparation without a prescription, however due to its euphoric and stimulatory effects it was soon widely abused by recreational substance users. Consequently, in 1959 supply of Benzedrine™ was restricted by the United States Food and Drug Administration requiring a prescription for its supply. Methamphetamine is structurally similar to amphetamine. In the late 1980s, crystal methamphetamine

"ice" was made readily available and manufactured through careful recrystallization of methamphetamine hydrochloride into quite large clear crystals with the superiority of being volatile enough to be vaporized unchanged for inhalational abuse.

ATS abuse is rapidly becoming a significant public health problem and understanding its toxicological effects on cardiovascular system is being recognized as an important priority by medical specialists and government agencies across the world. Globally, the prevalence of illicit drug use has been estimated at 5.2 % of the world population [3]. ATS users are the second most populous cohort of drug users globally [3]. In recent times, methamphetamine seizures have almost quadrupled and they continue to increase at an alarming rate [3]. Of the 144 tons of ATS seized globally in 2012, approximately half were seized in North America alone and a quarter in East and South-East Asia [4]. Almost half of the seizures in USA occur at the USA-Mexico border [4]. In USA, cocaine abuse is declining whilst the use of ATS is rapidly increasing [4]. The latest US Department of Justice National Drug Threat Assessment has reported that the methamphetamine prices are falling whilst its purity levels are increasing [5]. Methamphetamine is becoming more readily available and accessible in USA partly due to increasing production by small-scale methamphetamine laboratories. ATS abuse is particularly prevalent amongst younger individuals and it is rising at an alarming rate. Terplan et al. [6] observed that 8 % of pregnant women admitted to their obstetric unit in 1994 were methamphetamine users whilst this prevalence had tripled to 24 % by 2006. Number of individuals initiating methamphetamine use in the USA has also been rising substantially [5]. Recent studies from San Diego region have reported that the prevalence of patients with ATSAC requiring admission has risen from 1.8 % in 2009 to 5.6 % in 2014 [7]. ATSAC is also becoming more recognized and prevalent in the San Joaquin Valley region as 12 % of the patients that were diagnosed with cardiomyopathy had ATSAC [8].

There is increasing interest and need in understanding the association between exposure to ATS and development of cardiomyopathy, the pathogenesis and clinical course of patients with this emerging cardiovascular disorder. This is particularly tempted by increasing clinical encounters of patients with ATSAC and its usually delayed recognition together with absence of systematical analysis of the rapidly emerging body of knowledge on this specific cardiovascular condition.

Accordingly, a comprehensive and systematic review was performed to explore and collate the existing and emerging evidence relating to the association between ATS exposure and development of cardiomyopathy, potential biological mechanisms implicated in the pathogenesis of ATSAC, risk factors associated with development of ATSAC, clinical features and clinical course of patients with ATSAC.

Search Methodology

Electronic searches in Medline (with PubMed Interface), Embase, CINAHL and British Nursing Index Database (BNID) were performed using combination of the following key terms "Chemically-Induced Disorders", "Cardiotoxicity", "Toxicology", "Etiology", "Amphetamine", "Amphetamines", "Amphetamine-related Disorders", "Amphetamine-type Stimulants", "Methamphetamine", "Crystal Methamphetamine", "Khat", "Synthetic Cathinones", "Cardiovascular Diseases", "Cardiovascular System", "Cardiomyopathies", "Takotsubo Cardiomyopathy", "Heart Failure" and "Substance-related Disorders".

The abstracts and full texts of these articles were then reviewed by the author for relevance. An expanded search of the relevant articles was performed for identification of "grey literature" and involved hand searching of reference lists of all the relevant articles, use of PubMed related articles feature, searches in conference proceedings for unpublished literature and attempting to contact study authors for missing data and information when deemed required. A Google search for internet-based resources and open-access publications was also carried out. In order to include all the relevant literature, no filters were used during the electronic search. No language restriction was applied. The review was not restricted to any study designs. No age, gender, socioeconomic status or setting restrictions were applied. Full copies of the relevant articles were obtained and thoroughly reviewed by the author.

A total number of 30 studies detailing the association between ATS exposure and development of ATSAC were included after removal of duplicates and exclusion of 12 studies on the basis that they did not provide relevant data relating to association between ATS exposure and development of cardiomyopathy.

Association Between ATS Exposure and Development of Cardiomyopathy in Animal Studies

Development of cardiomyopathy following exposure to methamphetamine has been demonstrated reliably in animal experimental studies. Following 8 weeks of intraperitoneal methamphetamine hydrochloride injection in male rats appearance of similar myocardial lesions as those seen in

cardiomyopathy namely cellular degeneration, myocytolysis and formation of contraction bands in the subendocardium has been observed [9]. Left ventricular dilatation as well as systolic and diastolic dysfunction following methamphetamine injections based on a binge protocol has also been observed in rat models [10]. A recent study in male rhesus monkeys with long history of intravenous methamphetamine self-administration has also shown considerable reduction in ejection fraction at 12 weeks following exposure to methamphetamine challenge [11].

Case Reports of ATSAC

Since the 1970s, a total of 14 reports in the literature have shown the association between ATS use and development of cardiomyopathy (Table 1). In 1976, development of dilated cardiomyopathy in a 45-year-old female who had abused dextro-amphetamine orally in setting of chronic medicinal use was first reported [12]. In the 1980s, various case reports in the literature further demonstrated the link between ATS use and development of cardiomyopathy [13–16]. In 2008, Srikanth et al. [17] from University Medical Center in California reported the first case of stress-induced "Takotsubo" cardiomyopathy in a 42-year-old female following acute intranasal use of methamphetamine in setting of chronic abuse. The patient showed recovery of ventricular function over a period of days and weeks following initial inotropic and medical therapy. Grave consequences of delayed recognition of ATSAC have also been described by authors in case reports [18].

Case Series on ATSAC

To date, 8 case series have reported an association between ATS exposure and development of cardiomyopathy (Table 2). Overall, these case series comprise 91 patients with ATSAC from various regions of the world including USA, Australia, New Zealand, Iran and Belgium [19–26]. Majority of patients were male, young and various patterns of ATS exposure have been reported.

The first large case series was reported from Honolulu and included 21 patients [20]. Majority of patients were chronic users and inhalation was their preferred route of administration. Nineteen of these patients were evaluated with echocardiography and 16 were found to have enlarged left ventricular diastolic and left atrial dimensions. Twelve patients were also found to have enlarged right ventricular size. Majority of these patients had congestive heart failure with a mean ejection fraction of 25 % (range 9–50). Although most of the patients in this case series were discharged from the hospital, no data on their long-term outcomes were reported by the authors. In 2012, Sadeghi and her co-authors provided further support for the association between ATS abuse and development of severe left ventricular dysfunction amongst young patients. Regrettably, the patients in their series had grim outcomes with two patients showing no clinical or echocardiographic improvement after 5 months and one patient having such severe persisting symptoms that he had to be considered for cardiac transplantation [22].

In 2016, two relatively large case series have emerged from Australasia. Voskobonik et al. [25] from Melbourne

Table 1 Summary of case reports studies linking ATS exposure to development of cardiomyopathy

Author(s)	Year	Country	Study design	Gender	Age (years)	Type of ATS use disorder	Nature of ATS use	References
Smith et al.	1976	NZ	Case Report	F	45	Dextro-AMP	Oral	[12]
Call et al.	1982	USA	Case Report	F	22	AMP	IV	[13]
O'Neill et al.	1983	USA	Case Report	M	24	AMP (Acute)	IV	[14]
Ayres	1983	USA	Case Report	M	38	Dextro-AMP	Oral	[15]
Jacobs	1989	USA	Case Report	F	48	METH	Oral	[16]
Hong et al.	1991	USA	Case Report	F	34	METH (chronic)	Inhaled	[67]
Nishida et al.	2003	Japan	Case Report	M	51	METH (chronic)	NR	[74]
Crean et al.	2004	UK	Case Report	F	30	AMP (chronic)	Oral	[68]
Srikanth et al.	2008	USA	Case Report	F	42	METH (chronic)	Intranasal	[17]
Mizia-Stec et al.	2008	Poland	Case Report	M	20	MDMA (weekly)	Oral	[69]
Innasimuthu et al.	2009	UK	Case Report	M	34	AMP	Oral	[70]
Karch	2012	USA	Case Report	M	23	METH (chronic)	Inhaled	[18]
Bruno et al.	2012	UK	Case Report	F	29	METH (chronic)	NR	[72]
Stokes et al.	2016	AUS	Case Report	M	31	Crystal METH	Inhaled	[71]

M male, *F* female, *NR* not reported, *METH* methamphetamine, *AMP* amphetamine, *MDMA* 3,4-methylenedioxy-*N*-methylamphetamine, *IV* intravenous

Table 2 Summary of case series describing the association between ATS and development of cardiomyopathy

Author(s)	Year	Country	Study design	Gender	Age (years)	Type of ATS use disorder	Nature of ATS use	References
Croft et al.	1982	USA	Case Series	M	35	PPHD (chronic)	IV	[19]
				M	26	PPHD (chronic)	IV	
				M	36	PPHD (chronic)	IV	
				M	36	PPHD (chronic)	IV	
Wijetunga et al.	2003	USA	Case Series	M: 19/21	Mean age: 41	Crystal METH	Inhaled (19/21)	[20]
Jacobs	2006	Belgium	Case Series	M	31	AMP (chronic)	Intranasal	[21]
				M	34	AMP (chronic)	NR	
				M	24	AMP (NR)	NR	
Sadeghi et al.	2012	Iran	Case Series	M	28	METH (chronic)	NR	[22]
				F	29	METH (chronic)	NR	
				F	31	METH (chronic)	NR	
Hawley et al.	2012	US	Case Series (8 patients)	NR	NR	METH (NR)	NR	[23]
Fulcher et al.	2013	AUS	Case Series	F	36	METH (Acute)	Oral	[24]
				M	45	METH (Chronic)	IV	
Voskoboinik et al.	2016	AUS	Case Series	M: 14/20	Mean age: 35	METH and Crystal METH (duration of use ranged from 1 day of recreational use to 10 years of nearly daily use)	Inhaled, IV and Oral	[25]
Kueh et al.	2016	NZ	Case Series	M: 25/30	Mean age: 40	AMP (current or past use)	NR	[26]

M male, *F* female, *NR* not reported, *METH* methamphetamine, *AMP* amphetamine, *IV* intravenous, *PPHD* propylhexedrine (N.B. *structurally and functionally is similar to METH*)

have presented a series of 20 patients with ATSAC. Fourteen of the patients were male and they had a mean age of 35 years. The patients mostly used methamphetamine and crystal methamphetamine and duration of use ranged from 1 day of recreational use to 10 years of nearly daily use. ATS exposure was acquired via inhalational, oral and intravenous routes. Majority of the patients had dilated cardiomyopathy and notably nearly a third of patients were found to have Takotsubo cardiomyopathy and most interestingly these patients had the atypical basal variant of this condition. Six out of 20 patients were seen to have features of early recovery characterized by left ventricular ejection fraction greater than 50 % within 6-weeks post-initial diagnosis. Small left ventricular and left atrial size, short duration of ATS exposure and presence of atypical basal variant of Takotsubo cardiomyopathy were associated with favorable early outcomes.

A recent retrospective case series from Auckland has included 30 patients with ATSAC [26]. The investigators have also observed that majority of their patients were male (25 out of 30) with a mean age of 40 years. Considerable portions of patients in their study (19 out of 30) were of indigenous Maori ethnicity. This was accounted by higher prevalence of ATS exposure amongst indigenous populations or possibly an unrecognized genetic predisposition to development of ATSAC following ATS exposure amongst Maori population. Majority of the patients (24 out of 30) had features of severe left ventricular dysfunction and 15 of the patients had severe dilated cardiomyopathy. The investigators observed that severe left ventricular dysfunction persisted in patients despite optimal heart failure therapy and the rates of hospital readmission were relatively high. Overall five patients in this case series succumbed to mortality from end-stage heart failure which is remarkably high compared to other series.

Case-Control Studies on ATSAC

Within the past decade, five case-control studies from the USA have revealed an strong association between ATS exposure and development of cardiomyopathy (Table 3). Yeo and colleagues found that methamphetamine users had a 3.7-fold increased risk of developing cardiomyopathy and ATS use was associated with more severe reduction in left ventricular ejection fraction in comparison with non-users [27]. Similarly, ATS abusers from Hawaii were observed to have echocardiographic features suggestive of severe dilated cardiomyopathy compared with non-users [28]. Sutter and colleagues from Davis Medical Center in California reported that ATS use results in development of mostly dilated cardiomyopathy with severe reduction in systolic function in comparison with non-users [29].

Recent study of patients from southern California region has shown that the prevalence of ATSAC has significantly increased from 2009 to 2014 [7]. Close evaluation of 141 ATSAC sufferers indicated that continued ATS use was associated with worsening severity of cardiomyopathy including systolic function and functional status, whereas cessation of exposure to ATS offers the outlook of improvement in their functional status.

There has also been a considerable increase in prevalence and recognition of ATSAC in the Central valley region of California [8]. In a recent retrospective case-control study, including patients from the San Joaquin Valley, Kiel and colleagues were able to identify 121 patients with ATSAC. They noted that ATSAC patients were more likely to be young (mean age 49.7), Causation (66 out of 121) and male (93 out of 121) [8]. Similar to previous findings, ATSAC sufferers were once again found to predominantly have dilated cardiomyopathy with severe left ventricular dysfunction.

Biological Mechanisms Implicated in the Pathogenesis of ATSAC

Various authors have endeavored to further account for the association between ATS abuse and development of cardiomyopathy by providing pathophysiological explanations. This is further supported by the observation that some of the pharmacodynamic effects of ATS use such as tachycardia, hyper-stress and hyper-catecholamine states are themselves independently capable of leading to development of cardiomyopathy and they have been recognized as tachycardia induced cardiomyopathy (tachycardiomyopathy), stress induced cardiomyopathy (Takotsubo) and pheochromocytoma induced cardiomyopathy [30–32]. In addition, plausible mechanism(s) leading to development of cardiomyopathy in these conditions have been reviewed and presented in the literature [33, 34]. It is most probable that ATSAC shares in commonality some of the pathophysiological pathways leading to development of cardiomyopathy as seen in these conditions.

Furthermore, oxidative stress, accelerated apoptosis, increased p53 activity, necrosis, perfusion defects, fatty acid toxicity, altered cardiac gene expression, abnormal cardiac protein synthesis and function in addition to defects in intracellular calcium hemostasis have been implicated and suggested as potential mechanisms leading to development of ATSAC (Fig. 1).

Free radical production and promotion of myocardial oxidative stress appears to be a prevailing hypothesis for

Table 3 Summary of case-control studies describing the association between ATS and development of cardiomyopathy

Author(s)	Year	Country	Study design	Gender	Age (years)	Type of ATS use disorder	Nature of ATS use	References
Yeo et al.	2007	USA	Retrospective Case-Control Study	NSD	⇑ prevalence in younger patients ≤ 45	METH (ever)	NR	[27]
Ito et al.	2009	USA	Retrospective Case-Control Study	NSD	NSD	METH	NR	[28]
Sutter et al.	2013	USA	Prospective Case-Control Study	NSD	NSD	METH	NR	[29]
Sliman et al.	2015	USA	Retrospective Case-Control Study	M with ATSAC 79.3 % compared with 51.3 % in the all CHF patients	Mean age of ATSAC 51 compared with 72 in the all CHF patients	METH	NR	[7]
Kiel et al.	2015	USA	Retrospective Case-Control Study	ATSAC patients more likely to be male (M: 93/121)	ATSAC patients more likely to be young (Mean age: 49.7)	METH	NR	[8]

⇑ increased, *M* male, *F* female, *NR* not reported, *NSD* no significant difference between cases and controls, *METH* methamphetamine, *CHF* congestive heart failure

development of drug induced cardiomyopathy. It is thought that ATS cause oxidative stress through (1) their metabolism to catechols which subsequently form ortho-quinones that are then converted to reactive oxygen and nitrogen species through the process of redox cycling, (2) induction of hyperthermia, (3) mitochondrial dysfunction, (4) leucocyte activation plus recruitment and (5) increased activity of xanthine oxidase which acts as a source of free radicals; thus boosting oxidative cardiomyocyte injury [35–38]. It has been reported that the metabolites of ATS play a more profound influence on promoting oxidative stress and they do this in a time and concentration de-pendent manner [39]. It is also considered that not only does oxidative stress cause cell death, moreover, it affects myocardial integrity and function by adversely affecting the excitation–contraction coupling and calcium signalling mechanisms within the cardiomyocytes [40]. It has been revealed that reactive oxidative species (ROS) are capable of reducing myocardial contractility by desensitizing myofilaments in ventricular muscles to the changes in intracellular calcium concentrations through induction of cardiac troponin-T phosphorylation and activation of p90 ribosomal S6 kinase [41–43]. ATS are also capable of inducing hyperthermia which promote the process of ROS formation and cause further mitochondrial dysfunction [36]. The role of leucocytes in promoting oxidative stress has been suggested by the presence of inflammatory infil-trates (lymphocytes and macrophages) in the hearts of rats that were exposed to a binge regime of 3,4-methylene-dioxy-*N*-methylamphetamine (MDMA) [37].

Induction of apoptosis following exposure to ATS is found in various tissues such as neurons, spleen, thymus, endothelium and hepatocytes [44–47]. Accelerated myocardial apoptosis has also been observed following chronic catecholaminergic myocardial stimulation [48]. Methamphetamine has further been linked to promoting p53 activity in cells and thus triggering p53-mediated apoptosis [49, 50]. It is thought that apoptosis may play a significant role in development of cardiomyopathy in ATS users through mitochondrial dysfunction which itself is an integral regulator of apoptosis and capable of releasing cytochrome c with consequential activation of proteases and cardiomyocyte protein degradation [36]. Necrosis has also been implicated as an alternative process of cell death in ATS users [21].

Induction of myocardial perfusion defects by ATS is a further conceivable pathophysiological mechanism through which cardiomyopathy can develop in ATS users. This is supported by ATS' ability to induce states of increased myocardial oxygen demand—a consequence of their pressor properties—whilst concomitantly causing reduction in oxygen supply to myocardium through induction of microvascular and coronary artery spasm.

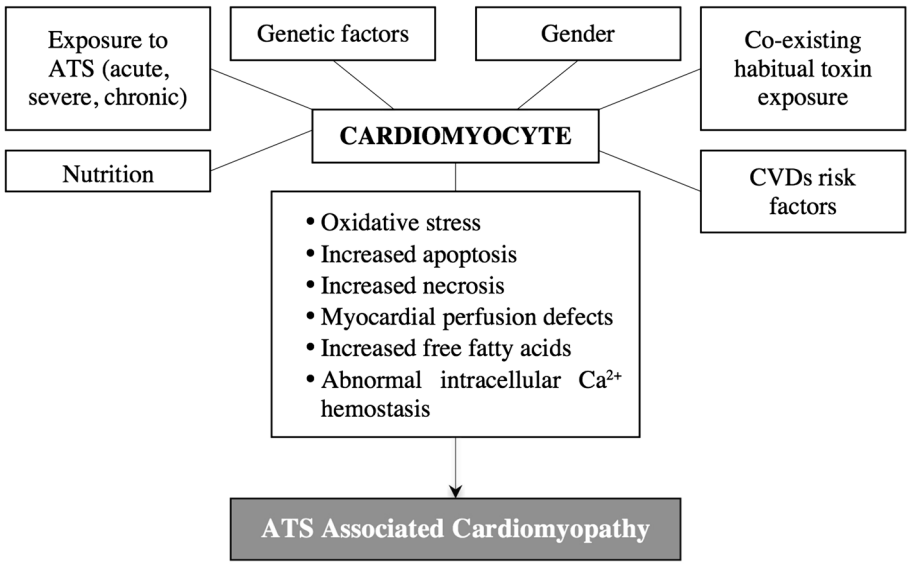

Fig. 1 Potential mechanisms causing cardiac toxicity in ATSAC. *CVDs* Cardiovascular diseases, Ca^{2+} calcium ion.

Profound global coronary microvascular spasm has been reported following exposure to methamphetamine [51]. In addition, significant ischemia due to coronary macrovascular spasm has also been reported in ATS users [52].

Chronically elevated levels of free fatty acids (FFA) have been associated with development of cardiomyopathy [53]. It is thought that cardiomyopathy results from both direct toxic effects of lipids and their accumulation within cardiomyocytes [54, 55]. It is also well established that activation of the sympathetic nervous system by ATS is capable of increasing circulating levels of FFA [56]. Accordingly, it can be postulated that raised FFA by ATS may also be an alternative mechanism leading to development of ATSAC. Although this hypothesis is probable, to date no studies are available in the literature that have conclusively tested this possible and alterative mechanism.

Altered cardiac gene expression, abnormal cardiac protein synthesis and function have been implicated as likely mechanisms in development of cardiac toxicity and cardiomyopathy following exposure to certain chemotherapeutic agents [57–59]. Other authors have also suggested possible existence of similar mechanisms in ATSAC [60]. There is certainly evidence that ATS are capable of altering genes expression in cultured rat cardiomyocytes [61]. However, there is currently lack of investigations and studies into the extent and mechanisms through which ATS are capable of causing cardiomyopathy by adversely affecting the structural and functional proteins within cardiomyocytes.

ATS exposure has been linked to considerable increases in cardiomyocyte intracellular calcium concentration [62]. There is evidence which points to a further deleterious impact of oxidative stress on myocardiocyte calcium hemostatic mechanisms [63]. Disruption in intracellular calcium hemostasis has been associated with fibrosis, hypertrophy and adverse myocardial excitability which are all likely to contribute to development of cardiomyopathy following exposure to ATS [64]. It is however, difficult to determine as to whether the increases in intracellular calcium levels are an independent mechanism or the consequence of disruption in intracellular calcium hemostatic processes due to other mechanisms.

It is likely that many of the biological mechanisms leading to development of cardiomyopathy following exposure to ATS work synergistically in the pathogenesis of ATSAC. In addition, certain individuals may have increased susceptibility to deleterious effects of mechanisms leading to ATSAC due to genetic polymorphism of enzymes involved in ATS metabolism, gender, nutritional deficiencies, coexisting alcohol and cigarette use and various other risk factors for cardiovascular diseases [29].

Risk Factors Associated with Development of ATSAC

Genetic predisposition has been suggested as a risk factor for development of ATSAC. CYP2D6 is a highly polymorphic enzyme which is involved in the initial and rate-limiting step during metabolism of methamphetamine. Evaluation of CYP2D6 genotype/phenotype has demonstrated a trend towards increased risk of developing heart failure in patients who are extensive metabolizers or have higher CYP2D6 activity scores [29]. Although CYP2D6 polymorphism may play a role in genetic predisposition for development of ATSAC in ATS users, the evidence is limited to a single study that only involved 37 patients in the control arm and there was only a demonstrated trend instead of a statistically significant difference.

It has been observed that there could be a racial vulnerability to the development of ATSAC amongst ATS users. This is supported by increased prevalence of ATSAC amongst Hawaiian and Filipino patients [20, 27, 28]. Mau and colleagues have reported that ATSAC is a significant underlying cause of heart failure amongst Native Hawaiians and other Pacific Islanders [65]. Furthermore, since more than half of the patients in the study by Kueh and his colleagues with ATSAC were indigenous Maori patients, it has been suggested that ethnicity may predispose patients to more severe form of cardiomyopathy and it also may be associated with worse prognosis [26]. Despite gathering support for the racial vulnerability for development of ATSAC amongst ATS users, the recent findings by Kiel and his colleagues have shown that Caucasian race is an independent predictor of ATS use in patients with cardiomyopathy [7, 8]. Currently, there is inadequate and inconsistent data to support a racial predisposition for development of ATSAC amongst ATS users although the weight of the existing evidence seems to be in favor of racial predisposition.

There is growing body of evidence which suggests that females with ATS exposure are more predisposed to development of Takotsubo type of ATSAC and in particular its atypical basal variant. This is supported by the findings in the recent study by Voskoboinik where 5 of the 6 patients with Takotsubo type ATSAC were female and had a shorter history of ATS exposure and all of them had the atypical basal variant of Takotsubo [25]. Remarkably, of the three other reported cases of patients with Takotsubo type of ATSAC in the literature, all of them have also been found to have the atypical basal variant of Takotsubo and two out of three of these patients were females which is particularly interesting given that most patients with non-Takotsubo type ATSAC are male [17, 24].

According to the current body of evidence, it appears that any pattern and route of exposure to ATS is associated with considerable risk of ATSAC. It may be plausible to consider that other factors that may influence the likelihood of developing ATSAC could include age at onset of exposure, frequency of exposure, lifetime duration of exposure, dose and purity of administered ATS, concurrent cocaine and alcohol abuse, exposure to other drugs, presence of nutritional deficiency and medical comorbidities which by themselves predispose individuals to acquired form of cardiomyopathy [66]. Further evidence is required to conclusively evaluate the role of these plausible risk factors for development of ATSAC.

Clinical Characteristics of ATSAC

Collated data from the identified case reports and case series in Tables 1 and 2 reveal that 76 % of patients with reported ATSAC in the literature have been male. Two of the five included case-control studies also indicate that men are more likely to be affected by ATSAC [7, 8]. Although there may be a male predisposition to development of ATSAC, nonetheless, the findings could be a reflection of greater prevalence of ATS abuse by men. Collated data from the identified case reports and case series indicate that the mean age of presentation by ATSAC patients is approximately 46.2 years. Three of the five included case-control studies confirm that ATSAC patients are mostly young at the time of presentation [7, 8, 27].

Current evidence indicates that most patients with ATSAC present late and with severe heart failure and systolic dysfunction. Based on the collation of available information in the case reports and case series, 79 % of patients with ATSAC were found to have presented with severe systolic dysfunction [12, 17, 19, 22, 25, 26, 67–71]. In the case series of Wijetunga, the mean left ventricular ejection fraction amongst ATSAC patients at the time of presentation was only 25 % [20]. In most case-control studies, ATS abuse was found to be associated with severe heart failure [8, 27–29]. Although these findings are very considerable, it needs to be appreciated that investigator reporting bias may have resulted in greater attention being drawn to ATSAC patients with more severe form of this disorder. Certainly with increased recognition and better surveillance for early detection of patients with ATSAC, a more accurate understanding of the virulence of ATSAC can be determined.

Majority of patients with ATSAC are observed to have dilated cardiomyopathy [12, 16, 18–21, 25, 67–72]. Sutter and colleagues observed that 70 % of their patients (14 out of 19) who had heart failure and history of ATS exposure on echocardiographic evaluation were found to have dilated cardiomyopathy [29]. Likewise, Kiel et al. [8] have reported that ATS users with heart failure predominantly have dilated cardiomyopathy.

It certainly appears that a subgroup of ATSAC patients also develops Takotsubo cardiomyopathy. Remarkably, all of the patients reported in the literature with Takotsubo type of ATSAC have been found to have its atypical basal variant form [17, 24, 25]. This may be explained by the relative abundance of adrenoreceptors at the ventricular base compared to the apex in the younger patients who are predominant users of ATS [73]. Only a single case of hypertrophic pattern of ATSAC has been described in the literature. It is necessary to give adequate consideration that in the aforementioned case, although during autopsy examination biventricular hypertrophy and endocardial thickening were observed, on microscopic examination typical findings of hypertrophic cardiomyopathy were absent [74].

Clinical Course of Patients with ATSAC

It is likely that ATSAC has a clinical spectrum of disease severity but since most reported cases have focused attention on patients at the end of this spectrum with severe disease, due to this limitation, it is difficult to accurately determine the clinical course of this illness at present time. Overall, patients with Takotsubo type of ATSAC appear to have much better prognosis than those with dilated cardiomyopathy [24, 25]. A better prognosis can also be expected in patients with dilated cardiomyopathy without signs of overt heart failure [75]. Absence of established pathological myocardial fibrosis is also associated with better outcomes. There is encouraging evidence in support of utilizing late-gadolinium-enhanced cardiovascular magnetic resonance imaging for detection of macroscopic myocardial fibrosis in ATSAC [76].

A number of in vivo studies suggest that ATSAC may be reversible following cessation of ATS exposure. In a study, after 12 weeks of daily intraperitoneal methamphetamine injection in 20 male Wistar rats the exposure was ceased and evidence of recovery of the sustained myocardial changes was observed as early as 3 weeks after withdrawal [77]. Based on these observations, the investigators suggested that it is possible that almost all ATS induced myocardial changes may be reversed following cessation of exposure with the exception of fibrosis. Recently, echocardiographic follow-up of male rhesus monkeys with long history of methamphetamine self-administration has shown considerable improvements in their left ventricular ejection fraction, left ventricle posterior wall thickness, end systolic volume, end diastolic volume and left atrium diameter following 52 weeks of cessation from ATS exposure [11].

These in vivo studies are also being supported by latest findings of clinical studies. In a recent retrospective case-control study, it has been shown that continued ATS use is associated with worsening clinical markers of ATSAC including left ventricular ejection fraction and functional status whilst cessation is certainly associated with improvement in functional status of patients [7]. Voskoboinik has recently reported on 1-year follow-up of 10 of ATSAC patients included in their series whom had global cardiac dysfunction at the time of initial diagnosis and did not show early recovery [78]. After 1 year, five of these patients revealed to have had normalization of left ventricular function, three had mild to moderate left ventricular dysfunction and three still continued to have severe left ventricular dysfunction. Although further research with respect to the prognosis of ATSAC patients is needed, the current evidence is supportive of considerable recovery following cessation of ATS exposure in most patients.

Future Directions

Animal studies, case reports, case series and case-control studies reveal that there is a nexus between ATS exposure and development of ATSAC. The nature of such an association needs to be further explored through well-designed, longitudinal studies with larger sample sizes and extended periods of follow-up. In pursuit of developing evidence for establishing a causal relationship between ATS exposure and development of ATSAC, it needs to be appreciated that ultimately such a body of evidence must be in conformity with the Hill's criteria for causation. Accordingly, future studies need to be particularly focused at developing evidence that enable for precise analysis of the strength of association between ATS exposure and development of ATSAC. They must be such that assessment of consistency of the findings in these studies can be performed. The studies must provide adequate evidence on the temporal association between ATS exposure and development of ATSAC whilst adequately accounting for relevant confounding variables.

Although the association between ATS exposure and development of ATSAC can be explained by various plausible biological mechanisms, nevertheless, future in vitro and in vivo exposure studies can provide additional insight into the precise mechanisms implicated in the pathogenesis of ATSAC and this can further strengthen the support for establishing a causal link between ATS exposure and development of ATSAC. Such laboratory studies can also be utilized for elucidating potential genetic risk factors associated with development of ATSAC, prognostication and studying efficacy and safety of various specific therapies.

There is an urgent need for investigating and establishing risk factors associated with development of ATSAC and creating risk models for predicting outcomes such as advanced heart failure or sudden cardiac death. Although the current evidence is suggestive of recovery following cessation of ATS exposure, nevertheless, it needs to be appreciated that irrefutable evidence is lacking.

ATS abuse is rapidly becoming a significant public health problem, whilst evidence-based preventative and early detection strategies of ATSAC are non-existent. In clinical settings, when unexplained cardiomyopathy is encountered, ATSAC needs to be considered as a potential diagnosis and timely steps for detection of ATS exposure should be instigated. Given that based on current evidence, ATS exposure is associated with ATSAC, it is reasonable to expect that clinical assessment of patients exposed to ATS would involve evaluation for detection of cardiomyopathy. There is currently lack of evidence on specific management regimen for ATSAC patients with acute heart

failure syndrome. There is considerable need for development of evidence-based management strategies in improving natural outcome, symptoms and functional capacity of ATSAC patients. All patients with ATSAC should promptly be referred to cardiology services for specialized assessment and management. It can be expected that a multidisciplinary model of care is likely to provide for optimization of cardiovascular care outcomes of ATS users. In this regard, close collaboration with addiction medicine specialists, psychiatrics and social workers should aim to assist the ATS users with addiction treatment, compliance with cardiovascular follow-up and care in addition to harm minimization from other risk activities including cigarette smoking, excessive alcohol intake and chronic malnutrition.

Conclusions

There is growing body of evidence which suggests that ATSAC is an acquired disease state characterized by otherwise unexplained cardiomyopathy in setting of ATS exposure. It is anticipated that with increasing prevalence of ATS use, its increased availability and purity, more young patients with ATSAC would require acute and long-term care and specialized services. At present time, most ATSAC patients are male, young and unexpectedly present to medical services with features of severe cardiac failure. Evidence suggests that interplay of various pathophysiological processes contribute to development of ATSAC. Although most patients are found to have dilated cardiomyopathy, a subgroup of patients who are predominantly female can present with Takotsubo type of ATSAC and in particular its atypical basal variant. Generally, it can be expected that patients with Takotsubo type of ATSAC would have good prognosis. At present time, the existing evidence suggests that some degree of recovery can be expected following cessation of ATS exposure by ATSAC patients, although presence of myocardial fibrosis is associated with worse outcomes.

Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest.

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