

Drug-induced myocardial infarction secondary to coronary artery spasm in teenagers and young adults

Menyar Ayman A El

Department of Cardiology and Cardiovascular Surgery, Hamad Medical Corporation Doha, Qatar

Correspondence:

Ayman Ahmed. El menyar,
E-mail:
aymanco65@yahoo.com

ABSTRACT

There is no published registry for drug-induced acute myocardial infarction (AMI) with subsequent patent coronary angiogram in teenagers. To highlight the mechanism and impact of drug-induced MI with patent coronary arteries among teenagers who have relatively few coronary risk factors in comparison with older patients, we conducted a review of the literature. In this review most of the pertinent published (English and non-English) articles through the Medline, Scopus, Cochrane Database of Systematic Reviews, and EBSCO Host research databases from 1970 to 2005 have been reviewed. Teenagers and young adults with AMI and subsequent patent coronary angiogram were included. In those cases drug-induced coronary spasm was highlighted. Among 220 articles (>12000 cases) related with AMI with normal coronary angiogram, 50 articles (~100 cases) reported the role of drug in AMI secondary to coronary artery spasm (CAS). There is no well-conducted trial for AMI secondary to CAS in young adults but only a series of case reports, and the diagnosis in most of cases was based on the clinical and laboratory findings without provocation. CAS was associated with 12 illicit substances in teenagers (i.e., cocaine, marijuana, alcohol, butane, and amphetamine). Smoking is not only the initiative but also might harbor other illicit substances that increase the risk for CAS. Cocaine-associated AMI is the most frequent in various research papers. CAS was reported with 19 types of medications (i.e., over-the-counter, chemotherapy, antimigraine, and antibiotics) without strong relation to age. Despite drug-induced AMI being not a common event, attention to smoking and drugs in teenagers and young adults will have major therapeutic and prognostic implications.

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Myocardial infarction (MI) at a young age is unusual and is mainly owing to congenital coronary anomaly, coagulopathy, premature atherosclerosis, coronary artery spasm (CAS) or is drug-induced. It is characterized by low mortality rates, less extensive coronary artery disease (CAD), good residual left ventricular function, and a favorable prognosis. Epidemiologic studies have shown significantly different risk profiles in young patients when compared with older patients. It is not clear whether MI at a young age can be considered an independent model of infarction or a more premature and accelerated aspect of the same atherosclerotic process observed in older patients. Drug-induced MI is not a common phenomenon and the underlying mechanism has been related with coronary spasm in the majority of cases. However, there is one published report for possible atherogenic consequences of long-term abuse of some drugs in young age.^[1,2]

CAS is a well-known cause of acute coronary events and arrhythmia in the young people. The underlying mechanism of increasing the vasospastic susceptibility of the coronaries in some people is still speculative; also, there is no clear predictor

for the severity of the spastic attack and its recurrence.^[3,4] Drug-induced AMI secondary to CAS in teenagers is mainly related to illicit substances such as cigarette smoking, marijuana smoking, alcohol intake, butane inhalation, and cocaine use. However, certain medications may be blamed as well (Table 1).

To highlight the mechanism and impact of drug-induced MI with patent coronary arteries among teenagers who have relatively few coronary risk factors in comparison with older patients, we conducted a review of literature, in which most of the pertinent published (English and non-English) articles through the Medline, Scopus, Cochrane Database of Systematic Reviews, and EBSCO Host research databases from 1970 to 2005 have been viewed. Teenagers and young adults with AMI and subsequent patent coronary angiogram were included. In those cases, drug-induced coronary spasm was highlighted. Among 220 articles (>12000 cases) related with AMI with normal coronary angiogram, 50 articles (approximately 100 cases) reported the role of drug in AMI secondary to CAS.

Table 1: Case-reports for drug-induced AMI secondary to coronary artery spasm

Drug user	Reference	Drug abuser	Reference
Pseudoephedrine	23 and 42	Cigarette smoking	4
Ergotamine tartrate	45	Marijuana smoking	8
Ephedrine	54	Butane inhalation	70
Sevoflurane	55	Toluene inhalation	73
Propofol	56	Glue sniffing	74
Diet pill containing ephedra	43 and 44	Alcohol	6
Thyroxine	50	Cocaine	7
Bromocriptine	52	Amphetamine	75
5-flourouracil	51	Ecstasy	76
Capecitabine	53	LSD	77
NSAID	46	Heroin	78
Alluprinol	47	Khat	82 and 83
Amoxicillin	48		
cinoxacin	49		
Sulprostone	84		
Sumatriptan	85		
Tegaserod	86		
Ergonovine	88		
Diclofenac	87		

There are no well-conducted trials for AMI secondary to CAS in young, but only a series of case reports, and the diagnosis in most of cases was based on the clinical and laboratory findings without provocation. CAS was associated with 12 illicit substances in teenagers (i.e., cocaine, marijuana, alcohol, butane, and amphetamine). Smoking is not only the initiative but also might harbor other illicit substances that increase the risk for CAS. Cocaine-associated AMI is the most frequent in various research papers. CAS was also associated with 19 types of medications (over-the-counter, chemotherapy, antimigraine, and antibiotics). Those substances either illicit or innocent have been reported to cause CAS by itself or as additive factor to smoking and were characterized by a relative young age.^[5-9] Despite drug-induced AMI being not a common event, attention to smoking and drugs in teenagers and young adults have major therapeutic and prognostic implications.

MI with Patent Coronary Arteries

The prevalence of MI with normal coronary arteries is approximately 5%. The incidence of coronary spasm is much higher in Japanese patients with angina pectoris (approximately 40%). Approximately 10% of all patients with AMI and nearly 20% of those under 35 years of age do not have coronary atherosclerosis demonstrated by coronary angiography or necropsy, or both. Around half of nonatherosclerotic AMI patients have angiographically normal coronary arteries.^[3,10,11] The possible mechanisms entitle poor angiographic technique so that a significant coronary arterial stenosis was missed, small vessel disease, hypercoagulable states, coronary embolism, coronary trauma, coronary vasospasm, coronary thrombosis, and endothelial dysfunction. Intravascular ultrasound studies documented atherosclerotic plaques that failed to encroach on the lumen of the involved coronary artery. In these patients, it was

hypothesized that one of these small, intramural atherosclerotic lesions had ruptured, thereby, leading to coronary arterial thrombosis that subsequently lysed, leaving the normal lumen intact. The provocation of CAS after MI and/or ventricular arrhythmias carries a high risk, so in most of cases the diagnosis was based on the patency of the coronaries during elective coronary angiogram in addition to the clinical and electrocardiographic evidence of acute coronary events.^[3,4,10,11-13]

Patent Coronary Vessels After MI in Young Age

Coronary spasm in this age group was not specifically studied, except in few and small-sized studies. Otherwise, the majority of cases with patent coronary vessels after MI have been discovered after routine angiogram. There was no provocative test done acutely in the majority of cases and the diagnosis was made according to the clinical and laboratory data. Zimmerman *et al.*^[1] studied 8839 patients with MI; only 294 (3%) were males aged less than 35 years and 22% of those had patent coronaries, whereas 34% out of 210 females less than 45 years had patent coronaries. In comparison with older patients, young patients often have normal angiography or nonobstructive lesion. Current smoking and positive family history of CAD are the risk factors in young patients, whereas older patients were more diabetic and hypertensive. The survival rate at 7 years was 90–84% in young male and female vs 77–75% in older patients.

Wolfe and Vacek^[14] reviewed 2400 patients after MI and found that 35 patients (1.5%) aged 35 years or less had a higher proportion of normal coronary arteries (14%). Di Mario *et al.*^[15] studied 586 consecutive patients with CAD. Only 51 patients (8.7%) were under 45 years. These patients were angiographically evaluated from 1 to 12 months after a first MI. (13.7%), three had “normal” coronary arteries; one presented an anomalous origin of the left circumflex artery from the right sinus. Glover *et al.*^[16] studied 100 patients of age less than 35 years and sustained MI, all underwent coronary angiography and showed that 7% had normal coronary, 4% with coronary anomaly, and 1% had vasculitis.

Da Costa *et al.*^[17] observed that only a minority of patients were shown to have coronary arterial vasospasm (15.5%), a hypercoagulable state secondary to a congenital condition or oral contraceptives (13.9%), collagen vascular disease with presumptive small vessel disease (2.2%), or coronary arterial embolism (2.2%). There was no obvious etiology for AMI with normal coronary arteries was discernable in 66.2% of their patient population. Ammann *et al.*^[18] hypothesized CAS after MI in 21 patients. In those patients there was a history of migraine syndromes in the majority and seropositivity for cytomegalovirus and Chlamydia in few cases.

Definition of Coronary Spasm

Maseri *et al.* described the clinical, electrocardiographic, and angiographic features of 138 patients with variant angina and

concluded that the syndrome is considerably more polymorphic than initially inferred by Prinzmetal *et al.* Variant angina is defined by the angiographic demonstration of spontaneous or induced coronary spasm in patients with rest pain. Electrocardiographic features may include ST-segment elevation or depression. Coronary vasoconstriction and dynamic coronary obstruction also are components of atherosclerotic CAD. Coronary angiography is the standard criterion for the diagnosis of variant angina when coupled with the clinical syndrome of angina pectoris at rest with transient ST-segment elevation. The intracoronary route of administration of methylergonovine for provocation of spasm is safe, sensitive, and specific.^[19-21] Provocative test might be dangerous in acute stages of MI, and this risk will be more evident in cases presented with ventricular tachyarrhythmia.

Mechanism of coronary spasm in teenagers

CAS is known to occur with or without underlying atherosclerotic lesion. However, a substantial number of patients have seemingly normal coronary angiogram results, although many within this subgroup have evidence of early atherosclerosis demonstrated by intravascular ultrasound examination or at autopsy. The mechanism of CAS is not related with whether the inducer is illicit or innocent, but it depends on how sensitive the vessels, the nature of the substance released, the presence of underlying pathology, the presence of other synergistic substance, the sympathetic response, the dose, and the duration of the inducer is. Most of illicit substances have been reported to cause intense coronary vasospasm when used alone or in combination. Those substances exaggerate the vasospastic activity of other drugs; enhance endothelium dysfunction, increase platelet aggregation, increase sympathetic activity, and decrease myocardial oxygen supply.^[22,23] Abnormalities of nitric oxide synthase and reduced bioavailability of nitric oxide may result in increased basal vascular tone, vasoconstriction, vasospasm, and in activation, adhesion, and aggregation of platelets with release of additional vasoconstrictors. CAS causes a disturbance in the endothelial function of the coronary arteries and plays a role in initiating coronary occlusion, which in turn perpetuates the thrombotic event and leads to MI.^[11,19-21,24]

Clinical Manifestations of Coronary Spasm

Patients with AMI and normal epicardial coronary arteries tend to be young and to have relatively few coronary risk factors, except that they often have a history of cigarette smoking. The clinical, laboratory, and electrocardiographic features of AMI are, otherwise, indistinguishable from those present in the overwhelming majority of patients with AMI who have atherosclerotic coronary heart disease.^[16,25,26]

CAS can be a cause of not only variant angina but also ischemic heart disease in general, including unstable angina, acute MI, and sudden ischemic or arrhythmic cardiac death.^[4,27-30] Ventricular tachyarrhythmias,^[30] paroxysmal atrial fibrillation,^[31] variable degrees of atrioventricular block^[32] and asystole,^[33] and recurrent syncopal attacks^[34] are encountered as a result of coronary spasm. Left ventricular dysfunction^[35,36] is also related

in some cases to CAS.

The risk of sudden death during 2 years increases from 6% to 42% for variant angina. The prognosis and outcome after coronary spasm are related to many factors, including the numbers and duration of the attacks, the degree and distribution of ST-segment deviation, the presence of T-alternans, ventricular arrhythmia, or high degree of arterioventricular block during the attack.^[30,31,37] The long-term prognosis for patients who have survived an AMI with normal coronary artery systems on arteriography appears to be substantially better than that for patients with MI and atherosclerotic coronary heart disease.^[38,39]

CAS in Drug User

Besides emotional stress, β -blockers and aspirin are well known to exacerbate the vasospastic episodes,^[40,41] some of over-the-counter medications have been reported with CAS and MI in low-risk population. Many case reports have proved that ingestion of pseudoephedrine (for cough), antimigraine, and dietary supplements containing ephedra are associated with coronary spasm.^[42-45] Hypersensitivity to antibiotics, nonsteroidal anti-inflammatory drugs, and alluprinol also might cause MI owing to coronary spasm.^[46-49] Thyroxine has been reported to cause CAS in rare cases.^[50] A clinically significant CAS during chemotherapy and during noncardiac surgery has been reported. Chemotherapy might cause myocarditis, but its role in induction of CAS still needs more explanations.^[51-53] The underlying mechanism by which induction of anesthesia can cause CAS is still not clear; it happened with different anesthetics, but a considerable number of patients were smokers and young.^[54-56]

CAS in Drug Abuser

Cigarette smoking

Current smokers have 20 times the risk of vasospastic angina compared with never-smokers. Smoking even a single cigarette has been demonstrated to produce CAS during angiography. Young females who are smokers have a fourfold to fivefold increase in risk for CAD compared with never-smokers. Passive environmental smoking results in a 25% increase in the risk of CAD and death, and is now estimated to be the third leading preventable cause of death after active smoking and alcohol abuse.^[4,57-59] Smoking is the most frequent trigger factor for CAS; however, it is not only the initiative but also the host for other substances to come into the scene as a vasospastic agent.^[4-7]

Cigarette smoking is a major independent risk factor for CAS and thrombosis associated with both plaque rupture and endothelial erosion. Smoking-associated vasoconstriction is mediated by an α -adrenergic increase in arterial tone and by smoking-associated increases in platelet and plasma vasopressin, vasopressin carrier protein, and oxytocin. Endothelium-dependent (flow-mediated) vasodilatation is impaired in smokers and passive smokers, and thus increases the vasospastic susceptibility of concomitant agents. Teenagers who smoke still harbor other illicit substances and should be considered at a

high risk for CAS. In USA, the percentage study of teenagers who have tried different illicit drugs revealed that marijuana constitutes 41%, inhalants 18%, ecstasy 13%, methamphetamines 11%, LSD 10%, cocaine 9%, and heroin 4%.^[4,60–62]

Alcohol

Epidemiological studies have shown higher rates of alcohol abuse in men younger than 40 with a first MI and higher rates of sudden death in heavy alcohol consumers. Alcohol and cigarette smoking have been shown to have additive effects on increasing the risk of coronary death, which suggests that both are important factors in the pathogenesis of abrupt coronary occlusion in patients with normal coronary arteries. It is well known that ethanol induces concentration-dependent vasospasm in coronary arteries.^[6,63,64]

Cocaine

Cocaine was mentioned in 30% of all drug-related visits to emergency departments. It is the most commonly used illicit drug among subjects seeking care in hospital emergency departments and the most frequent cause of drug-related deaths reported by medical examiners.^[7,62,65] The risk of acute MI is increased by a factor of 24 60 min after the use of cocaine in persons who were otherwise at relatively low risk. The occurrence of MI after cocaine use was unrelated to the amount ingested, the route of administration, and the frequency of use. Ventricular arrhythmias occur in 4–17% of patients hospitalized with cocaine-related MI. The pathogenesis of cocaine-related MI and infarction is probably multifactorial and includes one or more of the following elements: an increased myocardial oxygen demand in the face of a limited or fixed supply, marked vasoconstriction of the coronary arteries, and enhanced platelet aggregation and thrombus formation. Thrombolytics and propranolol use in cocaine-related MI have been associated with increase mortality; this addresses the priority of vasodilator in such cases of CAS.^[22,66]

Marijuana

Marijuana is the most commonly used illicit drug in USA.^[37] The percentage of youths aged 12–17 who had ever used marijuana is 20.6%. Smoking marijuana is a rare trigger of acute MI and ventricular tachycardia and fibrillation by inducing CAS. Those complications have been encountered in both young male and female patients after marijuana smoking, and the majority of those patients had either normal coronary arteries or minimal coronary irregularities. Marijuana affects coronary microcirculation, decreases coronary flow, and enhances ruptured coronary plaque with a thrombus formation.^[8,67]

Butane inhalation

Volatile substance abuse (VSA) deaths comprise an important proportion of all deaths in British young people, as death from any cause in this group is rare. Approximately 56% of all VSA deaths in the UK were associated with butane (lighter refills)—the highest numbers of deaths being among those aged 14–18, whereas the youngest child to die owing to VSA was aged

12.^[68,69] The cause of death was essentially cardiogenic as butane has been reported to cause MI,^[9,70] ventricular fibrillation, and asystole.^[71,72] The postulated mechanisms for MI are CAS and hypoxia,^[70] whereas the underlying mechanisms for VF are explained by the ability of butane to decrease the threshold for arrhythmia and to sensitize myocardium to catecholamines,^[9] and by its direct toxic effect on the myocardium in addition to the induction of CAS. Toluene (which is similar to butane) and glue-sniffing have been reported to cause MI with normal coronaries.^[73,74]

Amphetamine, ecstasy, and LSD

Cocaine, amphetamine, and ecstasy have similar adverse effects on the cardiovascular system, predominantly related to activation of the sympathetic nervous system, and all were reported as a cause of MI secondary to CAS. Coronary artery plaques played a role in the endothelial dysfunction resulting from amphetamine use, and that induction of coronary arterial spasm was the likely mechanism of amphetamine-related acute MI. Ecstasy is a derivative of amphetamine and has similar effects. Both amphetamine and ecstasy produce indirect sympathetic activation by releasing noradrenaline (norepinephrine), dopamine, and serotonin from terminals in the central and autonomic nervous systems.^[75–77]

Heroin

Yu *et al.* reported a 38-year-old man with AMI after intravenous heroin injections. He was considered not to be at high risk for CAD and his coronary arteriogram was normal.^[78] Sniffing purified heroin could induce coronary or cerebral vasospasm. These findings demonstrate that vasospasm could be induced by heroin itself.^[79,80] Enhanced parasympathetic activity also played a role in the initiation of coronary spasm.^[81]

Khat (herbal ecstasy)

Khat chewers are very common in certain countries (i.e., Yemen and Somalia). The psychostimulant constituent of Khat leaves is cathinone; this substance may cause coronary vasoconstriction, negative inotropy, and negative chronotropy. The major metabolite of cathinone after its ingestion (norephedrine) also causes coronary vasoconstriction comparable with that by cathinone. The coronary vasoconstriction by cathinone was not owing to an action on α_1 -adrenoceptors either directly or indirectly through noradrenaline release. Three repeated doses of cathinone displayed the same coronary vasoconstrictor responses, indicating a lack of tachyphylaxis, and therefore confirming that the response was unlikely to be owing to indirect sympathomimetic activity. Cathinone has vasoconstrictor activity, which is not owing to indirect or direct sympathomimetic activity. The precise mechanism for this vasoconstriction remains to be determined. The coronary vasoconstriction may explain the increased incidence of MI in Khat chewers, which may arise from coronary vasospasm.^[82,83]

Recommendations and Conclusion

Drug-induced MI secondary to coronary spasm is not common and warrants well-conducted trials. Drug abuse is a worldwide

problem with serious cardiovascular implications. Over the years, millions of dollars have been poured into prevention and treatment services, still the problem has not been solved yet. CAS, with its consequences in young patients, raises the crucial role of thorough history-taking in teenagers because teenagers who smoke still harbor other illicit substances and should be considered a high risk for CAS. This will help to expect and to treat promptly such cases in emergency room and during the induction of anesthesia. The risk stratification for noncardiac surgery might need reevaluation in young smokers. The priority should be given to vasodilators for treatment of illicit substance-induced MI. Attention to smoking and drugs in teenagers and young adults have major therapeutic and prognostic implications.

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