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Chapter 5

Cocaine Cardiac Toxicity: Revisited

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Additional information is available at the end of the chapter

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Abstract

Cocaine is a potent stimulant which affects cardiovascular system severely. The mechanism of cardiac toxicity depends on multiple factors. Cocaine increases sympathetic stimulation and causes excess catecholamine secretion. Besides, its indirect sympathomimetic effect also directly exerts cardiotoxic effect by different cellular, molecular, and ionic mechanisms, resulting in acute or chronic cardiovascular impairment. Cardiac arrhythmia and acute myocardial ischemia or infarction is the most common cause of cocaine-induced sudden cardiac death. Chronic cocaine abuse can develop sustained hypertension or myocarditis or cardiomyopathy leading to depressed left ventricular function. Therapy for cocaine induced cardiac toxicity generally includes use of benzodiazepine agents, nitric oxide mediated vasodilators, alpha blockers and even calcium channel blockers. Beta blockers are relatively contraindicated in acute settings of cocaine cardiovascular toxicity. Hypersensitivity reaction to cocaine is often manifested by infiltration of eosinophilic or mononuclear cells without myocardial cell damage. Vascular dissection, endocarditis, and tricuspid valvular abnormalities are some less frequent manifestations in cocaine-induced cardiac toxicity.

Keywords: cocaine, ischemia, atherosclerosis, cocaine cardiomyopathy, cocaine myocarditis

1. Introduction

Cocaine is a potent natural alkaloid derived from the leaves of South American Coca tree (*Erythroxylum coca*). It was known as one of the oldest stimulants that were used by the ancient Inca in the Andres Mountain for simultaneous acceleration of their heart and respiratory rate to counter the effect of low pressure of the mountain air in the 3000 B.C. [1]. The

drug was first extracted in 1859 by German alchemist Albert Niemen from the coca leaves. In the past, cocaine was considered a medicine. Austrian psychoanalyst Sigmund Freud used it as a medicine for sexual impotence and depression. However, once hailed as a magical drug, it is currently known as the most addictive substance on the earth [2].

Cocaine is the second most popular drug addiction after marijuana. According to National Survey of Drug Use and Health (NSDUH), cocaine abuse is most common in the young population between 18 and 25 years in the United States [3]. The data from 2011 Drug Abuse and Warning Network (DAWN) cocaine abuse involve 40% of the total cases of the drug misuse cases in the emergency department [4].

Pure cocaine can be abused by chewing coca leaves (*Erythroxylum coca*). However, the more popular way of cocaine abuse is smoking or snorting. On the street, the drug is available in hydrochloride salt form or as free base form. In order to prepare hydrochloride salt, pure white crystal-like cocaine powder is treated with acid solvent. Hydrochloride salt is most commonly snorted or taken through intravenous route as the salt is water soluble. On the other hand, free base cocaine is produced by mixing with ammonia and ether as solvent and then dried to a powder form. Free base is more pure and more addictive when it is smoked or snorted. Crack cocaine is the most commonly used form of free base form of cocaine. Crack cocaine is synthesized by heating cocaine hydrochloride and baking soda solution to form a hard rock like cocaine base. It crackles when smoked. Drug dealers usually cut cocaine mixing with some adulterants. These additive materials are added to the cocaine to enhance its effect as well as increasing the amount. Glucose, mannitol, laundry detergents, laxatives, local anesthetic like lignocaine, strychnine, amphetamine are very popular additives while making cocaine. "Speed ball" is a popular addictive substance where heroin is added with cocaine [5].

The drug can be absorbed through mucous membranes. The peak effect of cocaine is very fast when it is taken by inhalation or intravenous route. However, nasal insufflation of drug exerts a slower action as the peak serum concentration is reached after 30–60 minute. Cocaine itself inhibits its absorption due to its vasoconstriction effect [5]. Cocaine is rapidly metabolized in the body. Its serum half-life is 45–90 minute. Cocaine can be detected for several hours in the blood and urine sample after its use. It is metabolized into two major metabolites: benzoylecgonine and ecgonine methyl esters, which are capable of producing hypertension. Norcocaine is another minor metabolite, also known for its vasoconstrictive effects. Cocaine metabolites can be detected in the blood and urine sample even after 4 days of cocaine use. Hair analysis is a sensitive marker of detection of cocaine and its metabolites for chronic cocaine abuse [6].

2. Pathogenesis of cocaine cardiac toxicity

Cocaine abuse affects multiple organ systems including the neurological, cardiovascular, immune, and hematological systems simultaneously due to its complex pharmacological action. It binds to membrane-bound proteins, which include transporters, receptors, and voltage-gated ion channels.

- Generalized sympathomimetic activity

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Sympathomimetic effects of cocaine take place when it binds to three monoamine transporters of the nerve terminals: the serotonin transporter (SERT), the dopamine transporter (DAT), and the norepinephrine transporter (NET). Cocaine can bind also two neurotransmitter receptors: muscarinic and sigma receptors. Interaction with monoamine transporters along with neurotransmitter receptors lead to a cascade of cocaine-induced stimulation of central sympathetic outflow. Thus, it inhibits reuptake of the neurotransmitters from the extracellular space. The increased concentration of the neurotransmitter in the synapse causes enhanced postsynaptic transmission. As a result of sympathetic stimulation, cocaine causes vasoconstriction, hypertension, and increased myocardial oxygen demand [7] (**Figure 2**).

2.1. Cardiac arrhythmia

Pathophysiology of the cocaine cardiac toxicity further includes inducing cardiac arrhythmia, which is one of the very common causes of death in the emergency department. Cocaine-abuse-related cardiac arrhythmia is considered having multifactorial underlying causes.

- Increase in the concentration of catecholamine and generalized sympathomimetic effect is one of the causes of genesis of cardiac arrhythmia triggered by cocaine. Further cocaine-induced myocardial ischemia or infarction provides a potential substrate for arrhythmia [8] (**Figure 2**).
- Blockade of voltage-gated Na^+ and K^+ channels

Cocaine is capable of binding to cardiac sodium, potassium calcium channels at clinically significant concentration. Inactivation of voltage-gated sodium and potassium channel by cocaine leads to intracardiac slowing of conduction and myocardial suppression. In Guinea pig model, cocaine blocks ventricular fast voltage-gated Na^+ channels in a dose-dependent and reversible manner [9, 10]. These result in decreased myocardial contractility, cardiac arrhythmia, and decreased left ventricular ejection fraction. Prolongation of the cardiac ventricular depolarization period leads to reentrant arrhythmia. Bruguda syndrome like electrocardiographic pattern can be secondary to mechanism of cocaine-related Na^+ channel blockade [11] (**Figure 1**).

Besides, cocaine on Na^+ ion channels also causes blockade of potassium and L-type Ca^+ channels. The potassium current is significantly diminished following the drug abuse. Cocaine blocks the human ether–a-go-go-related gene (h-ERG) channel to delay the rectifier K^+ current (I_{kr}) and thereby inhibits repolarization phase of the action potential. Prolongation of the action potential results in QT prolongation in habitual cocaine users [12].

At a higher serum concentration, cocaine binds to protein with lower affinity as the proteins with high affinity get saturated. At lower concentration, high-affinity monoamine transporters are inhibited. It binds to voltage-gated ion channels at a higher concentration as monoamine transporters get saturated. In animal model, progressive cocaine poisoning at higher serum concentration demonstrates cardiotoxicity along with CNS effect [7].

- Ca^+ homeostasis

Cocaine-induced binding and opening of L-type Ca^{+} channels causes increase in intracellular Ca^{+} ion concentration due to ionic influx in cardiomyocyte in experimental model. The drug promotes opening of L type Ca^{+2} channels and decreases closing rate. Consequently, intracellular Ca^{+} level rises and also provides additional reason for cardiac arrhythmia by secondary messenger pathway [13].

Calsequestrin is a major Ca^{2+} storage protein in sarcoplasmic reticulum of the cardiac and skeletal muscle cells. Cocaine is capable of disrupting the excitation contraction coupling through prevention of polymerization of calseqestrin and its calcium binding capacity in sarcoplasmic reticulum of cardiomyocyte. As a result, it reduces sarcoplasmic reticulum Ca^{2+} storage and cytosolic release of Ca^{2+}, leading to cardiac arrhythmia [14] (**Figure 1**).

2.2. Myocyte damage

Cocaine causes myocardial damage by both direct and indirect pathway resulting in different morphological and histological abnormalities including contraction band necrosis, cardiomyopathy, myocardial fiber disarray, mononuclear cell infiltration, etc. [11] (**Figures 1** and **2**).

- Myocardial cell apoptosis

In animal model, cocaine is able to cause apoptosis of the myocardial cells in a dose- and time-dependent manner through mitochondrial pathway. It is found an increase of cytochrome c enzyme levels in the cytosol in comparison with its level in mitochondria in fetal rat myocardial cells exposed to different doses of cocaine for different time intervals. Cytosolic cytochrome c binds to apoptotic activating factor 1 (Apaaf 1) and d ATP. It produces activated caspase 9, which cleaves procaspase 3 to create active caspase 3. Cocaine is believed to cause apoptosis of the myocardial cells by increasing caspase protein activities in animal model. Furthermore, cocaine increases Bax protein levels and decreases Bcl 2 in vivo to increase caspase activity and mitochondrial cell death [11]. Myocardial cell apoptosis is also demonstrated by cocaine-induced rise of p38 MAPK (mitogen-activated protein kinase) and inhibition of cytoprotective extracellular signal regulated kinase [11]. Wang et al. proposed a role of TNF α in cocaine cardiotoxicity. Myocardial TNF α induces myocardial apoptosis through its action causing chronic heart failure in animal model [15].

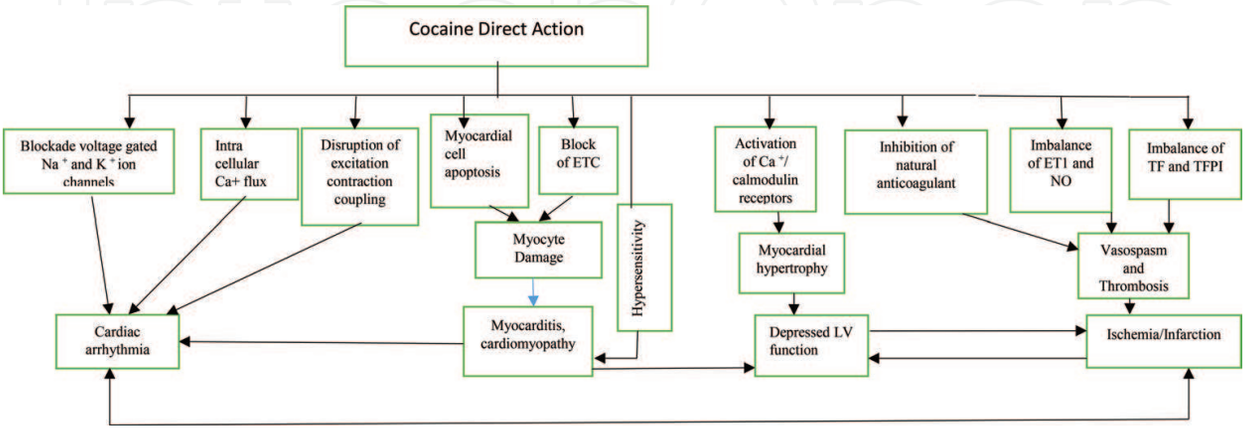

Figure 1. Schematic diagram of direct effect of cocaine in cardiotoxicity.

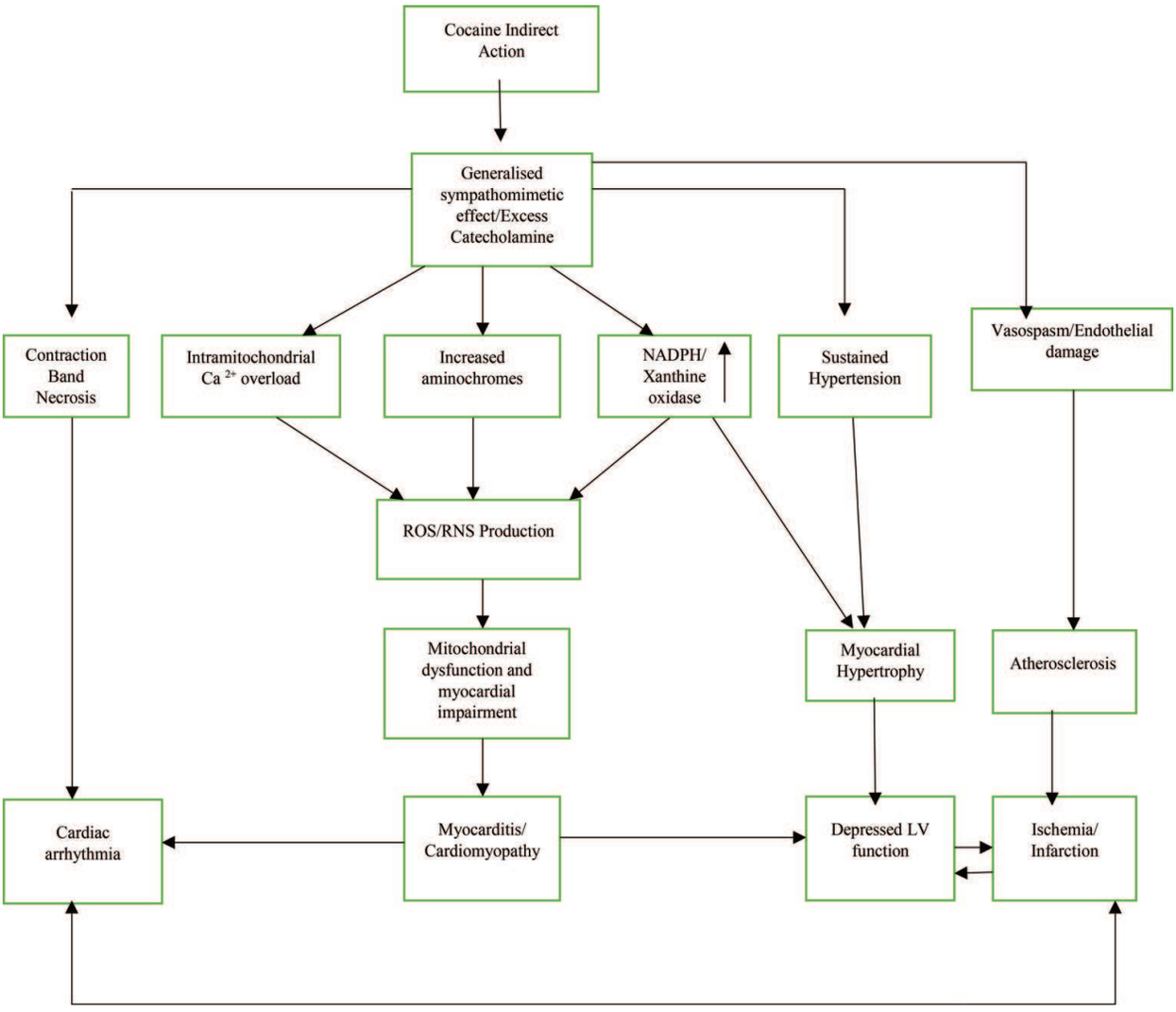

Figure 2. Schematic diagram of indirect effect of cocaine in cardiotoxicity.

- Mitochondrial dysfunction

Cocaine triggers indirect pathway of myocardial damage by production and accumulation of reactive oxidation species (ROS) and reactive nitrogen species (RNS) due to enzymatic or nonenzymatic catabolism of the cocaine-induced excess catecholamines, which causes mitochondrial damage and cell death.

Cocaine directly inhibits mitochondrial electron transport chain leading to decreased ATP production and formation of ROS and RNS. On the other hand, indirect release of high levels of circulatory catecholamines disrupts Ca^{2+} homeostasis. It results in a rise of intramitochondrial Ca^{2+} overload and depletion of ATP production. Moreover, catabolism of catecholamines produces different amino chromes (adrenochromes, dopachrome, and noradrenochrome), which are active sources of ROS. Further contribution of the mitochondrial ROS production is obtained from the increased NADPH oxidase and xanthine oxidase activity on high levels of catecholamines. Increased mitochondrial ROS and RNS cause mitochondrial dysfunction and subsequent cardiotoxicity [16].

2.3. Myocardial hypertrophy

It is developed from cocaine-induced sustained hypertension by sympathomimetic effect on the heart [17]. In addition, cocaine stimulates α 1 adrenoceptors to increase in total protein content along with β myosin heavy chain expression in the myocytes [18, 19]. Cocaine-induced production of ROS by stimulating α_1 adrenoceptors mediated by NADPH oxidase promotes hypertrophic growth ventricular myocytes [20, 21]. Finally, cocaine-induced direct activation of calcium/calmodulin receptors that culminates in increased phosphorylation of the ryanodine receptors leads to increased Ca^{+} release from sarcoplasmic reticulum and increase in protein formation in the myocytes [22] (**Figures 1** and **2**).

2.4. Effect on the blood vessels

- Atherosclerosis and vasospasm

Cocaine is known for developing premature atherosclerosis even in the young abuser (mean age 32 years) [23]. Cocaine and its metabolites induced sympathomimetic effect that leads to prolonged vasoconstriction (**Figure 2**). Endothelial damage secondary to vasoconstriction forms the basis of atherosclerosis. Increase of the histamine and heparin, secreted from increased mast cell, is considered to increase endothelial cell permeability [24]. Increased endothelial cell permeability secondary to cocaine and coco ethylene (formed following cocaine abuse along with alcohol intake) causes deposition of the low-density lipoprotein in the vasculature causing atherosclerosis [25].

Cocaine triggers endothelial production of endothelin 1 (ET 1). In animal study, ET 1 is shown to have vasoconstriction effect [26, 27]. Endothelium-derived nitric oxide (NO) is a potent vasodilator. The bioavailability and biological activity of NO is reduced due to reduced expression of endothelial NO synthase (e NOS) in presence of cocaine [28]. Cocaine in clinical concentration in abusers can cause significant imbalance between the concentration of the ET 1 and NO [11] (**Figure 1**).

- Thrombus formation

Kugelmas reported significant expression of the P-selectin protein on the platelet surface that activates alpha granules leading to formation of platelet thrombus. Intravenous administration of cocaine may cause significant expression of P selectin protein [29]. Hollander et al. in their study demonstrated cocaine-induced thromboxane release from activated platelets with a decrease in prostacyclin, an inhibitor of platelet aggregation [25].

Production of endogenous thrombosis and thrombolysis may be found through intranasal cocaine administration. It is associated with high level of plasminogen activating factor 1 (PAI 1) [30]. PAI 1 is released with α granules when platelet is activated. It contributes to thrombogenic activity by inhibiting fibrinolysis. Altered blood viscosity and increase in Von Willebrand factor, a glycoprotein secreted from the endothelial cells, also attribute to cocaine-mediated thrombogenesis [31].

Thrombus formation also results from the cocaine-induced increased expression of tissue factor (TF) and reduced expression of the tissue factor pathway inhibitor (TFPI) in the dysfunctional endothelial cells [32] (**Figure 1**).

Finally, cocaine inhibits formation of natural anticoagulant antithrombin III and protein C contributing to its prothrombotic property [25].

3. Pathology of cocaine cardiac toxicity

The morphological changes in the heart are attributed directly to cocaine toxicity as well as to indirect action of the excess catecholamine secretion. Apart from these, the hypothesis on myocardial changes can occur due to hypersentivity reaction to cocaine.

3.1. Contraction band necrosis

Excess catecholamine contributes significant changes in the myocardial fibers and that change is different from myocardial ischemia and infarction. The change or lesion is known as contraction band necrosis (CBN). It is also termed as myofibrillar degeneration and sometimes coagulative myocytolysis. CBN can be found in any circumstances related to catecholamine excess as well as in drowning, intracerebral hemorrhage, coronary artery occlusion sudden cardiac death, and in wide variety of drug overdose like amphetamine, MDMA, phenylpropanolamine, etc.

CBN is the earliest visible manifestation of excess catecholamine characterized by presence of individual necrotic myocardial cells surrounded by normal healthy myocells unlike ischemia where all myocells supplied by a single vessel are damaged. In addition, myofillaments are in register in ischemia unlike in CBN where myofillaments are fragmented forming eosinophillic clamps. CBN is a condition where myocytes are hypercontracted with sarcomeres of shorter length (less than 1.5 μm). Z lines get thickened and are often termed as "Contraction bands." However, CBN is also considered as ischemic change as it can be developed following coronary occlusion and then reperfusion of the ischemic cells. The underlying mechanism of formation of CBN is considered diverse; however, intracellular Ca^{+} overload mediated by catecholamine is largely responsible for such morphological alteration [33, 34].

3.2. Myocardial disarray

Cocaine abuse leads to degenerative and inflammatory changes of the myocardium. Myocardial disarray is characterized by oblique or perpendicular alignment of the adjacent myofibers and joined by short hypertrophied myobridges. It is often associated with CBN, interstitial edema, and focal myocardial fibrosis. CBN along with myocardial disarray, fibrosis can act as an anatomical substrate to trigger fatal cardiac arrhythmia causing sudden cardiac death [35].

3.3. Myocarditis and dilated cardiomyopathy

Virmani et al. in their autopsy study has confirmed cocaine-induced myocarditis is an important cause of death in cocaine abuse besides formation of CBN. Different cocaine preparations containing different adjuvants, different route of drug delivery, and chronicity of drug abuse could be the reason of different histopathological findings [36]. In cocaine-induced myocarditis, small foci of myocytes necrosis are scattered in different areas of the heart associated with infiltrations of lymphocytes. Under electron microscope, vacuolization of the sarcoplasmic reticulum and loss of myofibrils are found in the lesion. The mononuclear cellular infiltrations can be associated with various degrees of interstitial fibrosis. Biopsy specimen findings that include myocytes necrosis along with mononuclear cellular infiltration containing lymphocytes and monocytes secondary reaction to myocytes necrosis may be a result of acute cocaine-induced direct cardiotoxicity [37, 38]. Chronic cocaine abuse may lead to development of interstitial fibrosis and congestive heart failure [39].

However, mononuclear cell infiltrations as well as eosinophillic infiltration in the myocardium is also postulated as hypersensitivity reaction to cocaine or any contaminants along with cocaine. In such cases, the following features are characterized: (1) absence of myocytes necrosis, (2) absence of any myocardial hemorrhage, (3) lesions are of same age, and (4) not related to dose of the drug. Hypersensitive eosinophillic myocarditis is very often secondary to abuse of crack cocaine containing large amount of bicarbonate [33, 37].

Mere cellular infiltration in the myocardium does not indicate development of myocarditis. According to Dallas criteria, a lymphocytic infiltration without necrosis does not prove myocarditis [33].

Lymphocytic myocarditis serves also anatomic substrate for cardiac arrhythmia and ultimately develops a permanent dilated cardiomyopathy [37].

3.4. Myocardial hypertrophy

Cocaine user's heart weight found in autopsy studies is usually 10% heavier than mean weights predicted by a standard nomogram. ECG study also reaffirms the existence of ventricular hypertrophy in regular cocaine users. Hypertrophied heart includes hypertrophied myocytes, increased collagen deposition, perivascular fibrosis, and medial hypertrophy of small arterioles [17].

3.5. Myocardial infarction

Cocaine-induced vasospasm or vascular wall thickening causes arteriolar narrowing. In addition, its positive ionotropic and chronotropic effect leads to myocardial oxygen demand. Rise of heart rate and blood pressure after cocaine abuse also contributes to medial thickening of the intramyocardial vessels. Finally, atheromatous effect of cocaine contributes to significant narrowing of the coronary blood vessels, leading to acute myocardial ischemia and infarction. AMI with nonatherosclerotique coronary artery supports the hypothesis of coronary spasm and subsequently the thrombus formation with increased myocardial oxygen demand especially in acute drug intoxication setting [40].

4. Clinical manifestations of cocaine cardiac toxicity

4.1. Myocardial ischemia and infarction

Myocardial ischemia develops following cocaine abuse due to:

- Increased sympathomimetic effect leading to rise in heart rate and myocardial oxygen demand
- Focal vasospasm of the coronary artery
- Increased atherosclerotic changes of the artery.

There is a multifold increased risk of acute MI during initial 1 hour after the use of cocaine use even in low-risk patients. Acute MI is manifested in 0.7–6% abusers with cocaine-associated chest pain. The incidence is much higher (25%) in younger people aged between 18 and 45 years old especially in those who are associated with other cardiac risk factors. Cocaine-associated chest pain is often substernal and pressure like associated with atypical presentations like pleuritic chest pain, nausea, palpitations, syncope, and vomiting. AMI reported is more among chronic abusers than first-time users. Most often, the drug is abused by smoking, intravenous, or intranasal route. Both Q and non-Q wave infarcts were found in different studies. About one-third cases of cocaine-related AMI are associated with normal anatomy of the coronary artery due to focal vasospasm of the artery or thrombolysis subsequent to blockade. However, the presence of thrombi or atherosclerosis is also evident in different autopsy studies related to cocaine-related death. Besides, myocardial infarction and myocardial ischemia without chest pain are often manifested with ST-T wave abnormalities on the ECG. This syndrome is often associated with normal epicardial coronary artery with marked thickening of the walls of the intramural coronary artery. Chronic users of cocaine are also susceptible to coronary vasospasm. Prinzmetal's angina like ST segment elevation is demonstrated in some abusers during first 2 weeks of withdrawal from cocaine [37, 41, 42].

- Cardiac biomarker

Cocaine-associated myocardial ischemia is not associated with elevation of CK-MB. However, elevated CK is demonstrated in 39% of the 49 cocaine users due to rhabdomyolysis, muscular trauma, or intramuscular injection. However, troponins are more specific cardiac biomarkers for cocaine users followed by CK-MB and CK, which is not specific [41].

Usually, acute ischemia or infarction develops within 12 hour of cocaine abuse. Weber et al. proposed a 12-hour observation period for cocaine abusers. High risk patients are identified by the following four parameters [43].

- ST segment depression or elevation of 1 mm or more that persisted for more than 1 minute
- elevation of troponin biomarkers
- recurrent chest pain
- hemodynamic instability

- Therapy consideration

Cocaine-induced ischemia or infarction can be treated with oxygen, aspirin to prevent thrombus formation, and nitroglycerine to revert coronary spasm. Nitroglycerine is able to relieve the chest pain in approximately half of the cocaine users. Nitroglycerine abolished Ach-induced vasoconstriction in long-term cocaine users. Intravenous benzodiazepine is used to prevent hypertension, tachycardia, academia, and hyperthermia. Benzodiazepine is also used to relieve the anxiety and chest pain in cocaine abusers. Phentolamine, an alpha receptor blocker, can be used in acute coronary syndrome especially in hypertensive emergencies. In a study on 45 patients, phentolamine is able to abolish successfully tachycardia, hypertension coronary artery diameter, and coronary sinus blood flow. Phentolamine is also useful for the treatment of cocaine-induced chest pain and ST segment elevation. Heparin, clopidogrel, and glycoprotein IIb/IIIa inhibitors have been used to lyse thrombus. Calcium channel blockers are considered second-line treatment for not responding to benzodiazepines or nitroglycerine. Calcium channel blockers improve heart rate, blood pressure, and myocardial contractility of the patients. All beta blockers should be avoided in acute setting in cocaine users.

Percutaneous coronary intervention is more desirable in cocaine using patients associated with myocardial infarction. Angiography can be important guidance to detect presence of thrombus and obstructive disease. Coronary thrombectomy along with glycoprotein IIb/IIIa inhibitors is advisable during PTCA in cocaine-associated ST segment elevation myocardial infarction. Stent thrombosis is important complication in continued and noncontinued cocaine users within approximately 8 months of antiplatelet therapy with bare metal and eluting stents [37, 40, 41].

4.2. Cardiac arrhythmia

Fatal cases of ventricular tachycardia, ventricular fibrillation, and sudden death related to cocaine abuse are reported frequently. However, cardiac arrhythmia can be manifested with or without myocardial ischemia or infarction resulting from the drug abuse. Cocaine prolongs QT interval and sometimes develops QT prolongation associated with ventricular tachycardia or Torsade de pointes [37]. In hypertrophied myocardium QT interval dispersion (difference between the QT length in the lead where it is maximum and QT length in the lead where it is minimum) of more than 80 ms, there is a loss of synchronized depolarization developing reentrant arrhythmia [17]. Cocaine-related Na^+ channel blockade replicates electrocardiographic pattern of Bruguda syndrome and is associated with ventricular fibrillation, polymorphic ventricular tachycardia, and sudden death in young patients with morphologically normal hearts [6].

- Therapy consideration

There is no specific treatment available for cardiac arrhythmia secondary to cocaine abuse. Antiarrhythmic agents class I and III can be avoided as they can further prolong the QT interval [44]. Benzodiazepines can be beneficial to manage supraventricular and ventricular tachycardia and tachyarrhythmia by inhibiting the drug's central stimulatory effect. In addition, it can reduce anxiety and agitation in cocaine abusers. Most atrial arrhythmia can also be responded to sedative drugs. The second line of drugs could be calcium channel blockers [6].

Early onset of cardiac arrhythmia following intake of the cocaine can be treated by sodium bicarbonate, which can reverse Na^+ channel blockade caused by cocaine and normalize the acid base balance. Ventricular arrhythmia manifested after several hours of cocaine intake is usually associated with myocardial ischemia and traditional treatment could be appropriate in such cases [6, 25].

4.3. Congestive heart failure

In long-term and acute cocaine intoxication, cocaine causes systolic dysfunction of the heart due to left ventricular dilation, decreased contractility, and increased end-diastolic pressure. Dilated cardiomyopathy is a very common complication of chronic cocaine abuse [41]. Left ventricular apical ballooning in Takotsubo cardiomyopathy of the heart is also reported in chronic cocaine abuse [44]. In acute cocaine intoxication, myocardial contractility and ejection fraction are reduced to increase end diastolic pressure and end systolic blood volume [45]. Chronic cocaine abuse leads to left ventricular hypertrophy and prolonged deceleration time [46].

- Therapy consideration

Cocaine-induced heart failure significantly improved following cessation of cocaine intake. However, it can be aggravated following resumption of cocaine abuse. Beta blockers are avoided in acute setting. In long-term cocaine abuse, cardiac transplantation is not beneficial [41].

5. Miscellaneous clinical manifestations

5.1. Dissection of the blood vessels

Dissection of aorta and coronary arteries is not very common, but it is found in "Crack" cocaine abuser due to severe hypertension and catecholamine release. Aortic medial disease and sustained severe hypertension are the usual risk factors. Aortic dissection is initiated by transverse tears in the aortic wall. In aortic dissection, tears usually extend through the intima and at least halfway through the media. However, in spontaneous coronary dissection, the dissection plane lies within media or between media and adventitia. In coronary artery dissection, eosinophillic periadventitial inflammation is commonly seen [33].

5.2. Endocarditis and valvular heart disease

Occasionally, in intravenous cocaine abuse, bacterial endocarditis and tricuspid valvular heart disease is reported in the literature. The association of the bacterial endocarditis development might be due to poor hygiene and frequent drug injection. However, the possibility of pathological effect of the cocaine including endothelial damage and thrombus formation cannot be ruled out [33, 41].

5.3. Sudden cardiac death

Sudden cardiac death secondary to cocaine abuse is rarely due to AMI. In most cases, cardiac arrhythmia is due to complex multifactorial consequence of cocaine cardiac toxicity [47].

Isolated several single case reports show that acute cocaine fatalities are found very often in cocaine body packers and body stuffers [48, 49]. Body packers smuggle by ingesting or inserting packets of cocaine or any illicit drugs in several body cavities or orifices to conceal them from law enforcement officials as they cross the international borders, and the drugs are subsequently retrieved in the country of arrival. Internal concealment of cocaine very often poses serious life-threatening conditions among body packers, such as cocaine intoxication due to rupture of the drug packets. The most serious consequence of such acute drug overdose is very often sudden cardiac arrest, cardiac arrhythmia or myocardial ischemia, and infarction [50].

Sudden cardiac death is also found in chronic cocaine users where patient's conditions are complicated by poor underlying cardiovascular conditions including coronary artery disease, myocarditis, cardiomyopathy, etc. [49].

- Alcohol

Cocaine abusers use alcohol along with drug to enhance the euphoric effect of the drug. Simultaneous alcohol use increases the chance of sudden cardiac death by many folds. It is found that alcohol increases serum concentration of the drug by 30% if alcohol is consumed prior to nasal inhalation of cocaine. However, this effect is not found following intravenous administration of cocaine or if it is taken before alcohol consumption. Bioavailability of the drug is increased following alcohol-induced nasal vasodilation. In addition, hepatic conversion of the cocaine into cocaethylene in presence of alcohol results in prolonged cardiac toxicity. Coco ethylene is known for increasing heart rate and dysrhythmogenic. The long lasting activity of the metabolite is responsible for increased chance of cocaine-induced sudden cardiac death in presence of alcohol [6, 51].

- Tobacco smoking

Combined tobacco smoking and cocaine abuse is responsible for diminution of the effective diameter of the diseased blood vessels. Vascular stenosis most commonly results in acute myocardial ischemia or infarction [6].

- HIV infection

In cocaine addicts with HIV infection positive, a cumulative effect of cocaine and HIV infection are found in cardiovascular system. It includes increased frequency of coronary wall and adventitial infiltration, thickening of the intramyocardial coronary arteries, and myocarditis [52].

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