JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2017 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 70, NO. 1, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.05.014

REVIEW TOPIC OF THE WEEK

The Cardiovascular Effects of Cocaine

Ofer Havakuk, MD,[a,b] Shereif H. Rezkalla, MD,[c] Robert A. Kloner, MD, PhD[a,d]

ABSTRACT

Cocaine is the leading cause for drug-abuse-related visits to emergency departments, most of which are due to cardiovascular complaints. Through its diverse pathophysiological mechanisms, cocaine exerts various adverse effects on the cardiovascular system, many times with grave results. Described here are the varied cardiovascular effects of cocaine, areas of controversy, and therapeutic options. (J Am Coll Cardiol 2017;70:101–13) © 2017 by the American College of Cardiology Foundation.

In the summer of 1884, it seemed that a new era had emerged in medicine; with the application of dissolved cocaine powder to the cornea of a frog, the birth of local anesthesia was declared (1). The use of chewed coca leaves, either as a powerful stimulant or as a spiritual communication instrument with the Gods (through Incan *Kuka Moma*, Mother Coca, the goddess of health and joy), can be traced back as early as 2500 BC (2). Cocaine acceptance in European culture was somewhat delayed, though, probably because of its reduced effect after drying before shipment across the Atlantic. By the end of the 19th century, cocaine regained its former publicity when well known physicians such as Dr. Sigmund Freud recommended its routine use: "I take very small doses of it regularly against depression and against indigestion, and with the most brilliant success" (3). Unfortunately, despite the Harrison Narcotics Act of 1914 (banning the nonprescription use of cocaine), this misconception was present even in the 1970s (4), allowing a culmination of cocaine abuse with staggering numbers of more than 2 million users in the United States alone by 2007 (5). The myriad deleterious effects of cocaine on the cardiovascular system were soon recognized, whereas the pathophysiological mechanisms by which cocaine exerts its harmful effect continue to be explored (**Figure 1**). Here we describe the current knowledge on the complex relationship between cocaine and the cardiovascular system and try to draw specific recommendations on the optimal ways to cope with cocaine cardiotoxicity (**Central Illustration**).

PHARMACOKINETICS AND PHARMACODYNAMICS

Cocaine (chemically: benzoylmethylecgonine; structurally: 2-β-carbomethoxy-3-β-benzoxytropane) is a naturally occurring alkaloid extracted from the leaves of *Erythroxylum coca*, first isolated by the chemists Dr. Gaedcke and Dr. Nieman in 1860 (6). Cocaine is cleared through tissue uptake and is metabolized by liver and plasma esterases into active (e.g., norcocaine) and inactive metabolites (7) that are eventually excreted in the urine (8). The onset and duration of cocaine's effects depend on its route of use (**Table 1**), consequently varying its cardiovascular and hemodynamic effects. In general, the intravenous and inhaled (i.e., smoked) routes have a very rapid onset of action (seconds) and short-lived (30 min) duration compared with the mucosally absorbed (e.g., oral, nasal [i.e., snorted], rectal, vaginal) routes (9). The excretion of cocaine and its metabolites is not affected by cocaine's route of ingestion; the half-life

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Department of Cardiology, Keck School of Medicine, University of Southern California, Los Angeles, California; [b]Department of Cardiology, Tel Aviv Medical Center, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [c]Department of Cardiology and Marshfield Clinic Research Institute, Marshfield, Wisconsin; and the [d]Huntington Medical Research Institute, Los Angeles, California.
The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 17, 2017; revised manuscript received April 26, 2017, accepted May 8, 2017.

ABBREVIATIONS AND ACRONYMS

AD = aortic dissection
BP = blood pressure
ECG = electrocardiogram
HF = heart failure
LV = left ventricular
MI = myocardial infarction
NO = nitrous oxide
VF = ventricular fibrillation

of cocaine is usually 60 to 120 min and that of its metabolites is approximately 4 to 7 h (7). These half-lives can be considerably prolonged, however, with repeated dosing (10). Cocaine's hemodynamic effect is dose-dependent; early stages of toxicity induce heart rate and blood pressure (BP) elevation (10% to 25% of baseline); advanced stages show further elevations in heart rate and BP (although BP drop might be seen as a result of sustained tachyarrhythmias). In late stages, a significant depressive effect is found, with severe bradycardia and circulatory failure (11). Importantly, because some cocaine metabolites continue to be active, they might exert cardiovascular effects similar to those of the drug itself (12). The various pathophysiological mechanisms by which cocaine exerts its cardiovascular effects are described in **Table 2** (13–45).

HYPERTENSION

Cocaine potentiates acute sympathetic effects on the cardiovascular system (46), with consequent increased inotropic and chronotropic effects, and increased peripheral vasoconstriction (**Table 2**). This vasoconstrictive response is also affected by increased levels of endothelin-1 (16), impaired acetylcholine-induced vasorelaxation (17), deranged intracellular calcium handling (19), and blockade of nitric oxide (NO) synthase (18). Interestingly, NO was also found to serve as a mediator in catecholamine release by the central nervous system (47,48). Additionally, vasoconstriction of specific arterial beds was shown to be induced by the sodium-channel-blocking effect of cocaine (44). In a controlled clinical setting, the administration of intranasal 2 mg/kg cocaine produced an acute 10% to 25% elevation in mean arterial pressure (23).

Evidence for a potential induction of chronic hypertension in cocaine abusers is abundant; cocaine induces endothelial injury and increases vascular fibrosis (49). Furthermore, cardiac hypertrophy and kidney mesangial fibrosis were demonstrated in autopsies of cocaine abusers (50). Nevertheless, only a 20% prevalence of chronic hypertension was found in a study conducted in 301 cocaine abusers (51). Similarly, in the CARDIA (Coronary Artery Risk Development in Young Adults) study, investigating the long-term cardiovascular effects of substance abuse in 3,848 participants, no differences in the rates of chronic hypertension were noticed in the 1,471 cocaine abusers during a 7-year period compared with the rest of the cohort (52). There is a lack of data to explain this controversy.

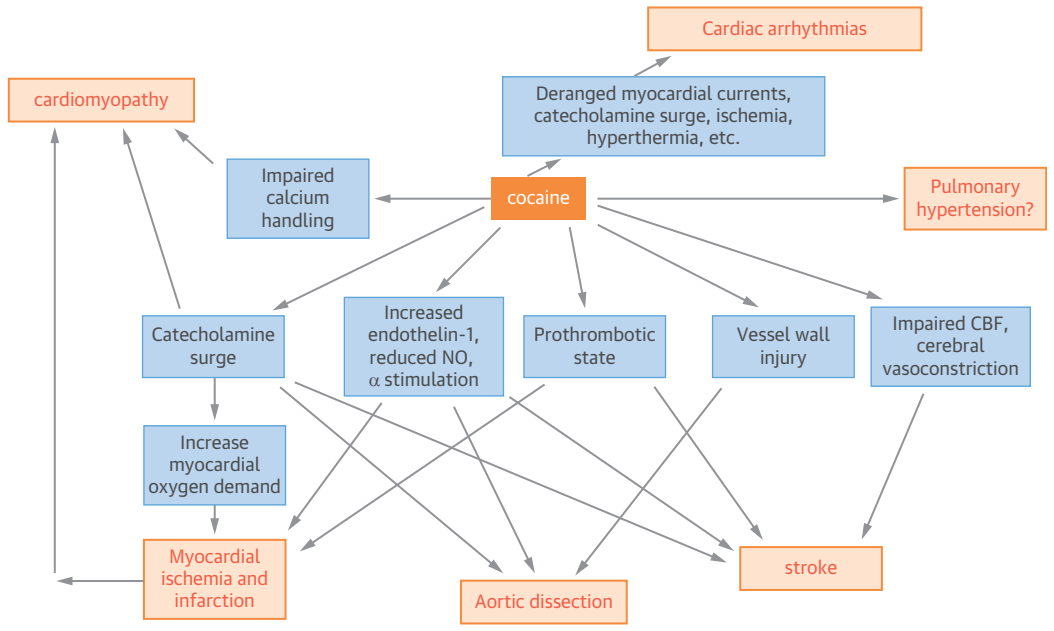
AORTIC DISSECTION

In the large International Registry for Aortic Dissection (IRAD), which collected data on acute aortic dissection (AD) from 17 international centers, the prevalence of cocaine abusers among acute AD cases was only 0.5% (53). However, 2 single-center studies (54,55) in the United States reported 37% and 9.8% prevalence of cocaine abuse in acute AD case series, most in young patients (mean age: 41 ± 8.8 years and 47 ± 6.8 years, respectively). Notably, the representation of blacks, an ethnic group at risk for both AD and cocaine abuse, in the U.S. registries was considerably higher than in IRAD (53–55). The pathophysiology behind cocaine-induced acute AD is multifactorial (**Table 2**). Cocaine was shown to induce vascular smooth muscle cell apoptosis and cystic medial necrosis, with consequent vessel wall weakening (20); a pathological finding that might also serve to explain cocaine-related coronary (29) and carotid (56) artery dissections. An echocardiographic study conducted in cocaine abusers showed a reduction in aortic compliance and an increase in thoracic aortic dimensions and stiffness compared with normal controls (57). Finally, the route of cocaine abuse needs to be considered; Hue et al. (54) reported that 13 of 14 patients with cocaine-related acute AD smoked crack cocaine. The rapid onset of action of smoked crack triggers an abrupt hemodynamic response, and its short duration of action induces frequent use in short intervals (58), consequently exposing the patient to repeated bouts of hemodynamic stress.

MYOCARDIAL ISCHEMIA AND INFARCTION AND THE APPROACH TO CHEST PAIN

The mechanism behind cocaine-induced myocardial ischemia includes increased myocardial oxygen demand as a result of an increased inotropic and chronotropic effect (15), which is inappropriately accompanied by coronary vasoconstriction and a prothrombotic state (**Table 2**). Accelerated atherosclerosis in cocaine abusers was demonstrated in an autopsy study comparing nonabusers with cocaine abusers who died from an acute coronary thrombosis (27). An increased number of mast cells per atherosclerotic coronary segment was shown in the cocaine abusers, suggestive of an increased local inflammatory state. However, an important confounder, cigarette smoking, was not adjusted between the study groups (27). Another large-scale autopsy study demonstrated significant epicardial coronary artery disease in 28% and small vessel disease in 42% of

FIGURE 1 **Cocaine's Cardiovascular Pathophysiological Pathways**

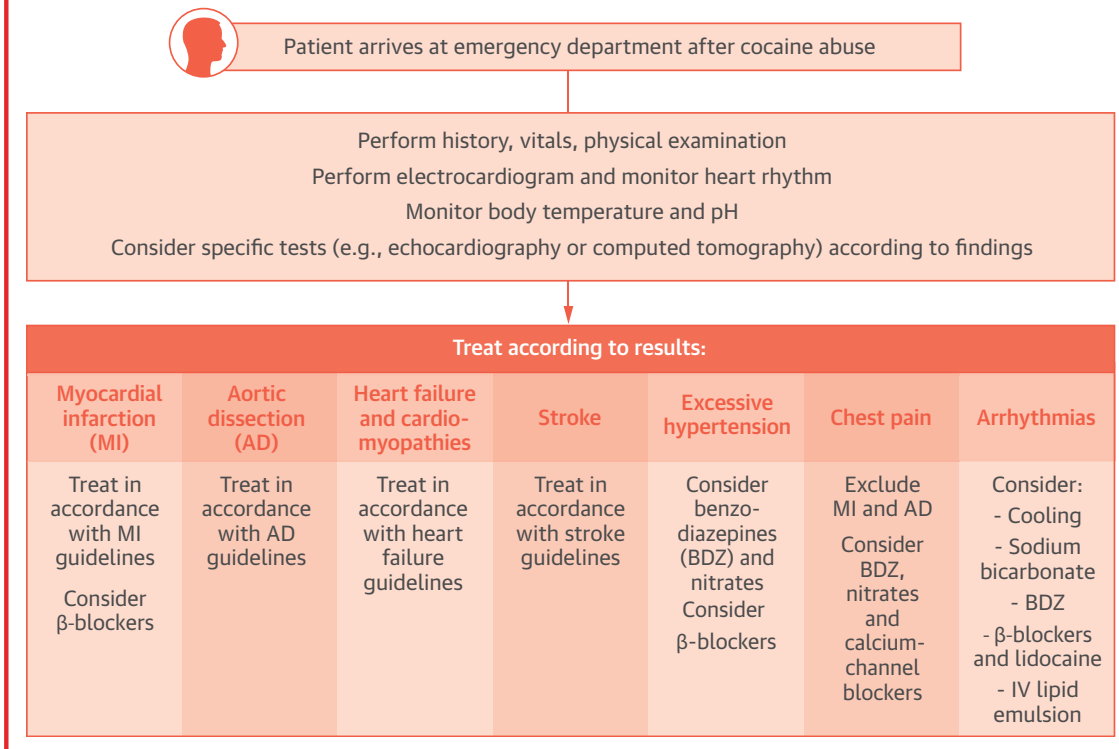


The ample cardiovascular effects of cocaine are exerted through a multitude of mechanisms, with possible consequent deleterious impact on almost every aspect of the cardiovascular system. CBF = cerebral blood flow; NO = nitrous oxide.

cocaine-related sudden deaths, despite a mean age of 34 ± 7 years (28) (although 81% were also cigarette smokers). An unusual mechanism for coronary thrombosis, plaque erosion, was also found in cocaine abusers (28).

Considering the deleterious effect cocaine can have on the oxygen supply/demand balance, it is not surprising that chest pain is the chief complaint in cocaine abusers presenting to emergency departments (59), and that the risk of myocardial infarction (MI) was found to increase up to 24-fold in the first hour after cocaine abuse (60). The correct diagnosis of cocaine-related MI, however, can be challenging; the majority of patients who present with cocaine-related chest pain demonstrate both an abnormal electrocardiogram (ECG) (61,62) and elevated creatinine kinase levels (62,63) (although cardiac troponin was found to more accurately identify cases of MIs (64)). Additionally, not all cocaine-related chest pain is cardiac; 2 large-scale registries (62,65) showed that the incidence of MI among cocaine abusers who presented with chest pain was only 6%, a finding that might correspond to extracardiac cocaine-related causes of chest pain (e.g., pleuritic, musculoskeletal) (66,67). Accordingly, a systematic approach has been offered to reduce unnecessary hospitalizations and interventions in these patients. Weber et al. (61) conducted a prospective study in 344 cocaine abusers evaluated for chest pain; patients with high-risk features (i.e., ST-segment deviation >1 mm, elevated cardiac troponin, recurrent ischemic chest pain, and hemodynamic instability) (**Figure 2**) were directly admitted (of whom 23% eventually developed MI). The remaining 302 patients were monitored in the emergency department with ECG and repeated cardiac troponin for a 12-h period before discharge. During a 30-day follow-up, no mortality occurred in the low-risk group, and only 1.6% developed MI (although 46 patients were lost to follow-up) (61). Because complications tend to occur early in the course of presentation, even when MIs do develop (68), these and other data (69) supported the safety of a 12-h observational approach in cocaine-related chest pain, an approach also suggested by the 2012 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on MI (70). It is important to note, however, that ST-segment elevations (from early repolarization) are prevalent in the demographic of cocaine users, making the definition of "high-risk patients" less reliable. The added value of more sophisticated tests in the investigation of

CENTRAL ILLUSTRATION The Approach to Cardiovascular Complications in Cocaine-Exposed Patients



Havakuk, O. et al. J Am Coll Cardiol. 2017;70(1):101–13.

Cocaine may provoke a variety of cardiovascular complications. A systematic approach toward the patient's clinical status including simple yet important initial tests can help with identifying and appropriately addressing these potential complications. AD = aortic dissection; BDZ = benzodiazepines; IV = intravenous; MI = myocardial infarction.

cocaine-related chest pain is questionable; results suggestive of clinically significant coronary artery disease were infrequently demonstrated with the use of either myocardial perfusion scans (2.3%, [71]) or coronary computed tomography angiography (10%, (72)), and did not significantly alter the management approach.

The mechanistic basis for treating cocaine-related chest pain with nitrates (73), phentolamine (an α-receptor blocker) (23), or verapamil (a calcium-channel blocker) (74) is derived from studies showing reversal of cocaine-induced coronary vasoconstriction with the use of each of these agents in the controlled setting of a cardiac catheterization laboratory. However, it is important to note that although cocaine-induced coronary vasoconstriction was demonstrated, none of the participants in these clinical studies actually developed chest pain, and, notably, each of these agents (including verapamil) induced a significant increase in heart rate (23,73,74), an effect that might further aggravate myocardial oxygen demand in cocaine-exposed patients.

β-BLOCKER THERAPY. Considering the known beneficial hemodynamic effects of β-blockers, the general approach toward β-blocker treatment after cocaine exposure was initially positive (75,76). Then, a case report in 1985 (77) suggested that the selective blocking of β-receptors might produce a paradoxical hypertension as a result of unopposed α-receptor stimulation. Animal studies (78,79) investigating possible protective agents against cocaine lethality in the early 1980s, which showed that pretreatment with

TABLE 1 Pharmacokinetics and Pharmacodynamics

Route of Use	Onset of Action(s)	Peak Effect (min)	Duration of Action (min)	Half-Life (min)
Intravenous	10–60	1–5	15–60	60–120
Smoked	5–10	1–3	5–15	60–120
Mucosal*	300–1,500	30–60	60–180	60–120

*Mucosal pharmacokinetics/dynamics can vary considerably, depending on the route of cocaine use (i.e., oral, nasal, and so on). Data presented in this table are from Inaba et al. (7), Ambre et al. (8), and Jufer et al. (10).

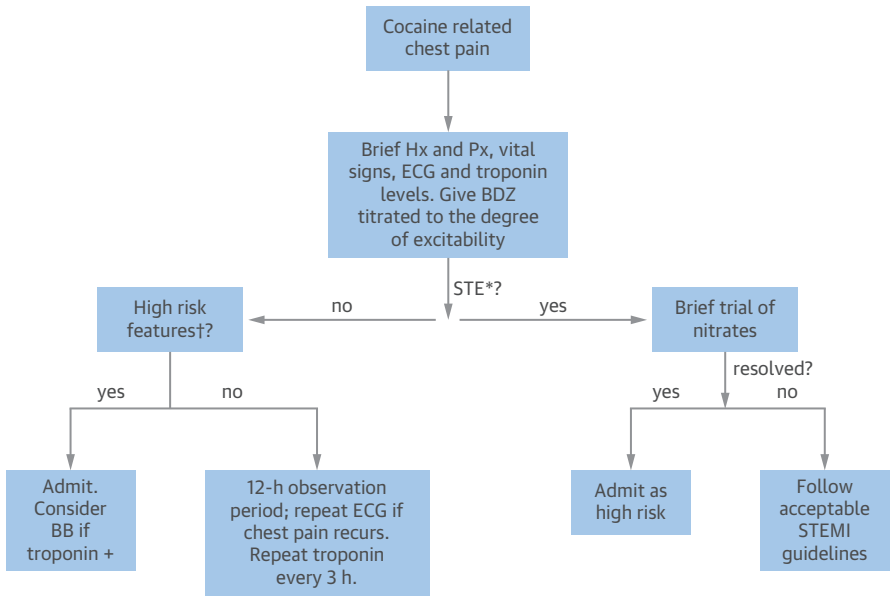
the β_1/β_2-receptor blocker propranolol failed to prevent seizure-induced mortality in animals exposed to escalating doses of cocaine, were misrepresented later as evidence for a suggested deleterious effect of propranolol in cocaine intoxication, even though propranolol was actually found to ameliorate the BP and heart rate elevations induced by cocaine in these trials (78,79). Another suggested deleterious effect of β-blockers is coronary artery vasoconstriction. A laboratory model of isolated porcine coronary artery rings showed that the combination of cocaine and propranolol induced increased arterial ring contraction (80). However, in this model, cocaine alone was not found to induce coronary artery vasoconstriction. A well-known clinical study tested the added effect of propranolol on cocaine-induced coronary vasoconstriction (81); in 5 of 10 patients who were exposed to propranolol after cocaine, no significant effect was noted. In the other 5, increased coronary vasoconstriction was demonstrated compared with cocaine alone; however, this result was mainly derived from a complete occlusion of the left circumflex artery in 1 patient, whereas nonstatistically significant changes were shown in the other 4. Furthermore, no BP or heart rate elevations were noted in the propranolol-treated patients (81). In anticipation of counteracting cocaine-induced coronary artery vasoconstriction by α-receptor blocking, the $\beta_1/\beta_2/\alpha_1$-blocker labetalol was used in patients who were initially treated with intranasal cocaine (82), and although labetalol did not worsen the cocaine-induced coronary vasoconstriction, its lack of effect further contributed to the growing perception of the inappropriateness of β-blocker therapy in cocaine intoxication. A case report describing cardiovascular collapse and death in a patient treated with metoprolol after consuming 1,000 mg of cocaine (83) has been suggested to exemplify the possible deleterious relation between cocaine and β-blockers, even though the patient did not experience a BP elevation after the metoprolol treatment and was

TABLE 2 Mechanism of Cocaine-Induced Cardiotoxicity

Cardiovascular Effect	Mechanism (Ref. #)
Hypertension	• Blockage of catecholamine reuptake in synaptic nerve endings (13) • Increased catecholamine release by the CNS (14). • Sensitization of post-synaptic response to catecholamine (15) • Increased levels of endothelin-1 (16) • Impaired acetylcholine-induced vasorelaxation (17) • Inhibition of NO synthase (with reduced NO levels) (18) • Impaired intracellular calcium handling (19)
Aortic dissection	• Acute hypertension as a result of an abrupt catecholamine surge (13–15) • Endothelial dysfunction (17) • Vessel wall injury (17) • Vascular smooth muscle cell apoptosis (20) • Cystic medial necrosis (21) • Concomitant cigarette smoking (22)
Myocardial ischemia and infarction	Increased myocardial oxygen demand (15): • Heart rate elevation • Increased contractility • BP elevation Coronary vasoconstriction: • α receptor stimulation (23) • Impaired intracellular calcium handling (19) • Impaired NO production (18) • Increased endothelin-1 levels (16) Prothrombotic effect: • Increased platelet activity and aggregation (24) • Elevated levels of fibrinogen and von Willebrand factor (25) • Increased plasminogen activator inhibitor activity (26) Accelerated atherosclerosis (27,28) Small-vessel disease (28) Plaque erosion (28) Coronary dissection (29)
Cardiomyopathy and HF	• Myocardial infarctions and scarring • Acute effect of catecholamine surge (13–15) • Impaired intracellular calcium handling (19) • Myocyte apoptosis (30) • Elevated levels of reactive oxygen species (31) • Eosinophilic myocarditis (30)
Arrhythmias	
Sinus tachycardia, AF, SVT	Increased sympathetic tone (13–15,32)
Ventricular ectopies	Increased sympathetic tone, myocardial ischemia (33)
Monomorphic VT	Myocardial infarction and scarring (34)
Long QT, TDP	Myocardial ischemia, inhibition of *KCNH2*-encoded potassium channels (35,36) inhibition of L-type calcium channels (36,37), cocaine-induced hyperthermia (38)
Bradycardia, conduction disturbances	Inhibition of voltage-gated sodium channels (i.e., Class IC antiarrhythmic effect) (36,39), nerve-blocking effect (40)
Brugada-type ECG	Inhibition of SCN5A sodium channels (41)
Pulmonary hypertension	Possibly through the adulterant levamisole (42,43)
Stroke	• Acute hypertension as a result of an abrupt catecholamine surge (13–15) • Endothelial dysfunction (17) • Vessel wall injury (17) • Prothrombotic effect (24–26) • Sodium-blocking effect (44) • Impaired cerebral blood flow (45)

AF = atrial fibrillation; BP = blood pressure; CNS = central nervous system; ECG = electrocardiogram; HF = heart failure; NO = nitric oxide; SVT = supraventricular tachycardia; TDP = torsade de pointes; VT = ventricular tachycardia.

FIGURE 2 The Approach to Cocaine-Related Chest Pain



To safely and effectively discriminate between benign and life-threatening chest pain in cocaine abusers, the evaluation of the patient's clinical condition along with electrocardiographic changes and elevation in cardiac troponin is suggested. Patients should be accordingly referred for urgent coronary angiography, hospitalization, or 12-h monitoring. *STE is defined as ST-segment elevation of ≥2 mm. †High-risk features: hemodynamic instability, positive cardiac troponin, recurrent chest pain. BB = β-receptor blocker; BDZ = benzodiazepines; ECG = electrocardiogram; Hx = history; Px = physical examination; STE = ST-segment elevation; STEMI = ST-segment elevation myocardial infarction.

also exposed to a high dose of cocaine (which might have been responsible for his late collapse). As a result of this notion, a scientific statement by the ACC/AHA on the management of cocaine-associated chest pain and MI in 2008 recommended against the use of β-blocker therapy in these patients (Class III, Level of Evidence: C) (84). However, either because of lack of adherence to guidelines or that not all patients disclose cocaine abuse when they are being treated by emergency teams, reports on large numbers of patients treated with β-blockers after cocaine exposure have been published and generally showed neutral or even beneficial effects on cardiovascular outcomes (85-87). Furthermore, prospective studies examining the safety of β-blockers in cocaine-exposed patients showed similar favorable results (88,89). The 2012 ACC/AHA guidelines state that nonselective β-blockers might be considered in persistently hypertensive or tachycardic patients after cocaine use, provided that they were treated with a vasodilator (Class IIb, Level of Evidence: C) (**Table 3**) (70). β-blockers represent an essential therapy in the mitigation of hyperadrenergic states, are known to reduce myocardial oxygen demand, and are considered lifesaving therapies in ischemic heart disease, heart failure (HF), and cardiomyopathies. The suggested hypertensive response as a result of an unopposed α-stimulation after β-blocker therapy in cocaine-exposed patients is either rarely seen or even usually found to be opposite. Interestingly, the severe hypertensive response found in 1 patient treated with the β_1-selective agent esmolol was successfully reversed by labetalol (90). Furthermore, indirect evidence for the safety of nonselective β-blockers in cocaine-induced coronary vasoconstriction can be drawn from a retrospective study in which the troponin rise was similar in patients who were or were not treated with β-blockers (86).

APPROACH TO COCAINE-INDUCED CHEST PAIN. Patients who present with cocaine-related chest pain should be first evaluated by history, physical examination, and vital signs, followed by an ECG and cardiac troponin. Patients who continue to have ST-segment elevation on their ECGs should be directly referred for coronary angiography with possible angioplasty and stent implantation (70). In cocaine abusers who received stent implantation,

the risk of stent thrombosis was increased (91), either from the prothrombotic effect of continued cocaine abuse or the lack of adherence to antiplatelet therapy, and thus, the type of stent selected should be considered accordingly. Although drug-eluting stents are occasionally used in the management of cocaine abusers (92), the majority of these patients usually receive bare-metal stents (93), and both the 2008 and 2012 ACC/AHA scientific statements recommend the use of bare-metal stents in cocaine abusers (70,84). In our practice, we deploy non-drug-coated stents, and if clopidogrel is used, we test platelet function before discharge to exclude clopidogrel resistance. Treatment with fibrinolytic agents in the setting of suspected acute MI should be balanced against the known cocaine-related risk of AD. Patients who show high-risk features (**Figure 2**) should be admitted with close monitoring. The vast majority of low-risk patients should be monitored with repeated ECGs and cardiac troponins for a 12-h period. In those who demonstrate hyperexcitable state with tachycardia and hypertension, intravenous benzodiazepines should be used (84). The choice between non-dihydropyridine calcium blockers, nitrates, α-receptor blockers, and β-receptor blockers is debatable. Patients with low-risk features can be treated with symptom-relief agents, such as nitrates. However, despite current guideline recommendations and after reviewing the data described earlier, we recommend consideration of nonselective β-blockers in both acute and chronic post-MI patients. Other agents, including antiplatelet and anticoagulant agents, should be used in accordance with accepted guidelines and with consideration of the risk of AD in cocaine abusers (**Figure 2**).

TABLE 3 The 2012 ACC/AHA Guidelines on Cocaine-Related Myocardial Infarction

Recommendation	Class of Recommendation	Level of Evidence
Administration of sublingual or intravenous NTG and intravenous or oral calcium-channel blockers is recommended for patients with ST-segment elevation or depression that accompanies ischemic chest discomfort after cocaine use.	I	C
Immediate coronary angiography, if possible, should be performed in patients with ischemic chest discomfort after cocaine use whose ST-segment remains elevated after NTG and calcium-channel blockers; PCI is recommended if occlusive thrombus is detected.	I	C
Fibrinolytic therapy is useful in patients with ischemic chest discomfort after cocaine use if ST-segment remains elevated despite NTG and calcium-channel blockers, if there are no contraindications, and if coronary angiography is not possible.	I	C
Administration of NTG or oral calcium-channel blockers can be beneficial for patients with normal ECGs or minimal ST-segment deviation suggestive of ischemia after cocaine use.	IIa	C
Coronary angiography, if available, is probably recommended for patients with ischemic chest discomfort after cocaine use with ST-segment depression or isolated T-wave changes not known to be previously present and who are unresponsive to NTG and calcium-channel blockers.	IIa	C
Administration of combined α- and β-blocking agents (e.g., labetalol) may be reasonable for patients after cocaine use with hypertension (systolic blood pressure >150 mm Hg) or those with sinus tachycardia (pulse >100 beats/min) provided that the patient has received a vasodilator, such as NTG or a calcium-channel blocker, within close temporal proximity.	IIb	C
Coronary angiography is not recommended in patients with chest pain after cocaine use without ST-segment or T-wave changes and with a negative stress test and cardiac biomarkers.	III	C

Data presented in this table are from Anderson et al. (70).

ACC = American College of Cardiology; AHA = American Heart Association; ECG = electrocardiogram; NTG = nitroglycerin; PCI = percutaneous coronary intervention.

CARDIOMYOPATHY, MYOCARDITIS, AND HF

A case report published as early as 1911 described acute and protracted HF in a previously healthy young woman exposed to cocaine before tooth extraction (94) (although MI cannot be decisively excluded in retrospect). Although myocardial scarring is considered a principal cause for left ventricular (LV) dysfunction in cocaine abusers, animal (95) and human (96) experiments showed that the administration of intracoronary cocaine caused an acute elevation in LV pressures, LV dilation, and reduction in contractility. These results correspond with case reports of cocaine-exposed patients experiencing an acute onset of HF with angiographically normal coronary arteries (97,98). Similarly, chronic HF and LV dysfunction have been documented in cocaine abusers without ischemic heart disease (99). The pathophysiology behind these findings (**Table 2**) includes cocaine-induced adrenergic surge (46), a condition linked to pheochromocytoma-induced cardiomyopathy and Takotsubo cardiomyopathy (reported in cocaine abusers [100]). Laboratory models showed that the exposure of myocardial fibers to high levels of cocaine induced a negative inotropic and lusitropic response (101). This effect was suggested to be mediated through the local anesthetic property of cocaine, with consequent alteration of intracellular calcium levels (101), a model reinforced by the comparable negative inotropic effect of another sodium-blocker, flecainide (102). The chronic exposure of cardiac myocytes to norepinephrine was shown to induce myocyte apoptosis through β-receptor and superoxide dismutase activation (31). Conversely, cocaine-induced myocardial hypertrophy was blunted with the use of the α receptor blocker prazosin (103). An elaborate report on the histological and immunohistochemical findings in cocaine-induced cardiomyopathy versus idiopathic dilated cardiomyopathy showed a significant increase in myocyte volume and reactive oxygen species levels in

cocaine-induced cardiomyopathy, even though macroscopic magnetic resonance imaging results were comparable between the 2 groups (104). Cocaine was shown to induce myocarditis, either through elevated levels of catecholamines, creating myocardial necrosis and local immune reaction, or from the induction of eosinophilic myocarditis (30). Autopsy case series of suspected cocaine-related mortality showing myocarditis prevalence ranging between 4% and 20% (105,106) have been reported.

ARRHYTHMIAS

Remarkably, a comprehensive document published in 1988 (107) concluded that cocaine-induced cardiac arrhythmias are infrequent and not well established. Nevertheless, considering the high prevalence of normal-appearing hearts in cocaine-related mortality cases (108), arrhythmic death is probably of considerable significance, and is exerted through varied mechanisms (**Table 2**).

Cocaine-induced heightened sympathetic tone is related to an increased risk of cardiac arrhythmias (32,109). Combined with the induction of myocardial ischemia and prolonged cardiac repolarization, this heightened sympathetic tone might induce ventricular ectopies, QT interval prolongation, torsade de pointes, and ventricular fibrillation (VF) (33,68). Myocardial lesions caused by cocaine-induced myocarditis might produce ventricular arrhythmias, either in the acute phase (as a result of increased excitability) or after recovery (scar-mediated from myocardial fibrosis) (110).

Cocaine acts as a potent myocardial ion-channel blocker of sodium, potassium, and calcium currents. The inhibition of the voltage-gated sodium channels produces a reduction in the rapid upstroke of the cardiac action potential, with conduction slowing and even complete inexcitability (39). Because this "class IC-blocking effect" is use-dependent (i.e., blocking effect is more significant when the channel is more active), the tachycardia induced by cocaine might serve to exacerbate sodium-channel blockade. Cocaine's sodium-blocking effect might also augment myocardial dispersion of repolarization in susceptible individuals, producing typical Brugada-type coved ST-segment elevation and VF predisposition (36). Interestingly, a dose-dependent effect of cocaine on sodium channels was noted; in a case series of cocaine-related cardiac arrests, cardiac asystole versus Brugada-type ST-segment elevation and VF was found in patients exposed to high versus low doses of the drug, respectively (41). Sodium-channel blocking effects were shown to be intensified under circumstances often found in cocaine abuse; increased acidity, either as a result of local ischemia or from the systemic effect of cocaine (111), was shown to increase cocaine's effect on sodium channels (112). Similarly, cocaethylene, a byproduct of cocaine and alcohol, aggravates the inhibition of cardiac ion channels (113). Opposed to the effect of sodium channels on depolarization, the inhibitory effect of cocaine on the repolarizing KCNH2-encoded potassium channel produces QT interval prolongation, early afterdepolarizations, and ventricular tachyarrhythmias (35). As in the case of sodium channels, alcohol ingestion and cocaethylene production increases potassium-channel blockage and QT prolongation (114), effects that might be aggravated by the ingestion of methadone, a QT-prolonging drug often used by cocaine abusers (115). A more complex effect is shown with myocardial L-type calcium channels; action potential shortening through calcium-channel activation versus action potential prolongation through calcium-channel inhibition was demonstrated with low versus high doses of cocaine, respectively (37,116). Put together, high doses of cocaine will prolong the QT interval through the drug's inhibitory effect on both potassium and calcium channels, while simultaneously causing bradycardia because of blockade of sodium channels, a condition known to predispose to torsade de pointes.

Cocaine-induced hyperthermia, either from a hypermetabolic state (117) or as a result of impaired heat dissipation (38), is another important systemic effect of the drug. In humans, cocaine-induced hyperthermia occurred in "clinically relevant" doses (2 mg/kg) and was worsened with escalating amounts (118). A variety of electrocardiographic changes and cardiac arrhythmias was demonstrated in cocaine-related (78) and non-cocaine-related (119) hyperthermia. This mechanism might explain the increased prevalence of cocaine-associated mortality in warm environments (118). Finally, the nerve-blocking effect of the drug might directly affect the autonomic nervous system with nerve blockade and paradoxical bradycardia (40).

APPROACH TO COCAINE-INDUCED ARRHYTHMIAS. The patient's general condition first needs to be evaluated, including the degree of excitability, body temperature, hemodynamic stability, pH levels, and the presence of ischemia (40). An immediate ECG along with continued ECG monitoring during the initial period of evaluation is recommended. QT interval prolongation should be sought and electrolyte imbalance corrected. In the case of hyperthermia,

cooling should be initiated. Sodium bicarbonate treatment may target 2 important components of cocaine toxicity, counteracting cocaine's sodium-blocking effect, while simultaneously correcting increased acidity (120). The heightened sympathetic tone, which is both central and peripheral, should be addressed with benzodiazepines, with varying degrees of sedation according to the patient's condition (84). We believe that nonselective β-blockers represent a useful treatment option in that scenario. Because most patients will react well to the aforementioned approach, antiarrhythmic drugs will not usually be needed, and should be used with caution. Because of the similar mechanism of action of Class 1A/1C drugs with cocaine, these medications should be avoided (112). Lidocaine might represent a safe alternative in the case of protracted ventricular arrhythmias (121). Data on the safety and efficacy of amiodarone is lacking (122). Intravenous lipid emulsion therapy, originally attempted in severe local anesthetic poisoning (123), was also shown to be helpful in extreme cases of cocaine intoxication (124). The therapy works by lipid compartmentalization of a lipophilic agent, and might also offer an abundant source of energy to the exhausted myocardium. Because cocaine is lipophilic and acts as a local anesthetic, it seems reasonable to apply this therapy in severe cases of cocaine poisoning. However, although current cardiopulmonary resuscitation guidelines recommend consideration of this therapy in severe local anesthetic poisoning, it is not suggested for cocaine intoxication (125).

PULMONARY HYPERTENSION

A retrospective study in 340 patients with pulmonary hypertension (126) demonstrated that patients with idiopathic pulmonary hypertension were 10 times more likely to have a history of stimulant drug use compared with patients with pulmonary hypertension and a known risk factor. Nevertheless, specific data on cocaine-induced pulmonary hypertension are less conclusive. A study examining the acute effect of intravenous cocaine on the pulmonary vasculature showed that cocaine did not produce an elevation in pulmonary artery pressure (127); however, chronic crack cocaine smokers were found to be at an increased risk of pulmonary hypertension (128). This inconsistency might be settled through several mechanisms. First, in contrast to other stimulants (e.g., methamphetamines), cocaine only mildly elevates the level of serotonin (129), a known agent in the induction of pulmonary hypertension. Second, both noradrenaline and dopamine were shown to have an equivocal effect on pulmonary vascular resistance (130,131). Third, addressing the specific effect of smoked crack on pulmonary artery pressures, levamisole, an adulterant often found in the mixed powder of crack, is converted after inhalation to aminorex, a substrate strongly related to drug-induced pulmonary hypertension (43). Finally, both the increased prevalence of cigarette smoking and the inhaled crack might predispose cocaine users to chronic lung injury, with subsequent increased risk for pulmonary hypertension.

VASCULITIS

Cocaine-induced midline destructive lesions have been infrequently described (132,133) and can be attributed to severe vasoconstriction, ischemic nasal mucosa, repeated traumatic damage caused by insufflated cocaine crystals and recurrent local infections, but also to antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis, with local findings similar to granulomatosis with polyangiitis (formerly Wegener) disease (133). Another type of ANCA-positive cocaine-related vasculitis takes a more systemic form, with fever, purpuric skin lesions, acute kidney injury, and glomerulonephritis (134). Importantly, the correlation between cocaine and vasculitis is confounded as both types of vasculitis were found to be related to the adulterant levamisole, an agent that was shown to induce the production of autoantibodies (133,134). A more exclusive association between cocaine and vasculitis awaits further investigation.

STROKE

Single-center registries have demonstrated an increased prevalence of cocaine abuse in both ischemic and hemorrhagic stroke patients (135,136), which tended to be more significant in the young (<60 years) age group. Similarly, a logistic regression model in >3,000,000 hospitalized patients identified cocaine abuse as a risk factor for either ischemic (odds ratio: 2.03; 95% confidence interval: 1.48 to 2.79) or hemorrhagic (odds ratio: 2.33; 95% confidence interval: 1.74 to 3.11) stroke (137). The mechanisms involved in cocaine-related stroke include acute hypertension (15), endothelial dysfunction and vascular injury (17), a prothrombotic state (24), impaired cerebral blood flow (45), and cerebral artery vasoconstriction induced by cocaine's sodium-blocking effect (**Table 2**) (44). A case-control study comparing 1,090 stroke patients with 1,152 controls showed that although an overall similar proportion of participants

in both groups were exposed to cocaine ("ever-users"), the timing of cocaine use (<24 h) was significantly related to stroke occurrence (138). Although important, these results are confounded by the higher prevalence of cardiovascular risk factors in the stroke group and by the absence of stroke in past users of cocaine in the control group. Notably, only 26 of the 1,090 stroke cases were related to acute cocaine use, an observation that corresponds with previous trials demonstrating an inconsistent relationship between cocaine and stroke risk (139). The 2013 AHA guidelines for the Early Management of Acute Ischemic Stroke (140) recommend the use of a urine toxicology screen in "selected patients," whereas the 2015 AHA guidelines for the Management of Spontaneous Intracranial Hemorrhage (141) recommend a toxicology screen in all patients. The impact of cocaine abuse on survival in hemorrhagic stroke patients has been inconsistent, with 1 study showing excess mortality (142), whereas another showed outcomes comparable to those of nonusers (137). In a small, retrospective study, 29 of 87 patients with cocaine-related ischemic stroke were treated with tissue plasminogen activator. Safety and efficacy outcomes were similar to those for non-cocaine-related ischemic stroke (143).

CONCLUSIONS

Cocaine abuse represents a considerable threat to the integrity of the cardiovascular system (**Figure 1**). In contrast to other addictive drugs (e.g., heroin, methamphetamines) that exert their harmful effects through a limited mechanism, cocaine has a multitude of pathophysiological pathways by which it affects the cardiovascular system. Unfortunately, cocaine is also highly addictive, and was found to significantly influence animal (144) and human behavior (145), a condition that might further influence patients' outcomes. Discouraging reports on the contemporary prevalence of cocaine abuse in teenagers, and even in children (146), might serve to increase awareness of the possible deleterious future effects of this perilous agent.

ADDRESS FOR CORRESPONDENCE: Dr. Robert A. Kloner, Huntington Medical Research Institutes, 10 Pico Street, Pasadena, California 91105. E-mail: robert.kloner@hmri.org. OR Dr. Ofer Havakuk, The Cardiovascular Division, Keck School of Medicine, University of Southern California, 1510 San Pablo Street, Los Angeles, California 90033. E-mail: Ofer.havakuk@med.usc.edu.

REFERENCES

1. Gärtner G. Die Entdeckung der Lokalanästhesie. Vienna, Austria: Der neue Tag, 1919.

2. Cartmell LW, Aufderheide AC, Springfield A, Arriaza B. The frequency and antiquity of prehistoric coca-leaf-chewing practices in Northern Chile: radioimmunoassay of a cocaine metabolite in human-mummy hair. Lat Am Antiq 1991;2:260–8.

3. Freud S. A contribution to the knowledge of the effect of cocaine, Vienna Medical Weekly, January, 1885. In: Byck R, editor. Cocaine Papers. New York, NY: Stonehill Publishing Co., 1974.

4. Hammond WA. Coca: its preparations and their therapeutical qualities with some remarks on the so-called "cocaine habit." In: Byck R, editor. Cocaine Papers. New York, NY, 1974:177–93.

5. Drugs, brains, and behavior: the science of addiction. National Institutes of Health, National Institute on Drug Abuse. 2014. National Institutes of Health Pub No. 14-5605. Available at: https://www.drugabuse.gov/sites/default/files/soa_2014.pdf. Accessed May 10, 2017.

6. Wohler V. Fortsetzung der Untersuchungen über die Coca und das Cocaïn. Justus Liebigs Annalen der Chemie 1862;121:372–5.

7. Inaba T, Stewart DJ, Kalow W. Metabolism of cocaine in man. Clin Pharmacol Ther 1978;23:547–52.

8. Ambre J, Fischman M, Ruo TI. Urinary excretion of ecgonine methyl ester, a major metabolite of cocaine in humans. J Anal Toxicol 1984;8:23–5.

9. Perez-Reyes M, Di Guiseppi S, Ondrusek G, Jeffcoat AR, Cook CE. Free-base cocaine smoking. Clin Pharmacol Ther 1982;32:459–65.

10. Jufer RA, Wstadik A, Walsh SL, Levine BS, Cone EJ. Elimination of cocaine and metabolites in plasma, saliva, and urine following repeated oral administration to human volunteers. J Anal Toxicol 2000;24:467–77.

11. Gay GR. Clinical management of acute and chronic cocaine poisoning. Ann Emerg Med 1982;11:562–72.

12. Hawks RL, Kopin IJ, Colburn RW, Thoa NB. Norcocaine: a pharmacologically active metabolite of cocaine found in brain. Life Sci 1974;15:2189–95.

13. Jones SR, Garris PA, Wightman RM. Different effects of cocaine and nomifensine on dopamine uptake in the caudate-putamen and nucleus accumbens. J Pharmacol Exp Ther 1995;274:396–403.

14. Venton BJ, Seipel AT, Phillips PE, et al. Cocaine increases dopamine release by mobilization of a synapsin-dependent reserve pool. J Neurosci 2006;26:3206–9.

15. Egashira K, Morgan KG, Morgan JP. Effects of cocaine on excitation-contraction coupling of aortic smooth muscle from the ferret. J Clin Invest 1991;87:1322–8.

16. Wilbert-Lampen U, Seliger C, Zilker T, Arendt RM. Cocaine increases the endothelial release of immunoreactive endothelin and its concentrations in human plasma and urine: reversal by coincubation with σ-receptor antagonists. Circulation 1998;98:385–90.

17. Havranek EP, Nademanee K, Grayburn PA, Eichhorn EJ. Endothelium-dependent vasorelaxation is impaired in cocaine arteriopathy. J Am Coll Cardiol 1996;28:1168–74.

18. Mo W, Singh AK, Arruda JA, Dunea G. Role of nitric oxide in cocaine-induced acute hypertension. Am J Hypertens 1998;11:708–14.

19. Perreault CL, Morgan KG, Morgan JP. Effects of cocaine on intracellular calcium handling in cardiac and vascular smooth muscle. NIDA Res Monogr 1991;108:139–53.

20. Su J, Li J, Li W, Altura B, Altura B. Cocaine induces apoptosis in primary cultured rat aortic vascular smooth muscle cells: possible relationship to aortic dissection, atherosclerosis, and hypertension. Int J Toxicol 2004;23:233–7.

21. Ramondo AB, Mistrorigo F, Angelini A. Intimal hyperplasia and cystic medial necrosis as substrate of acute coronary syndrome in a cocaine abuser: an in vivo/ex vivo pathological correlation. Heart 2009;95:82.

22. Wilmink TB, Quick CR, Day NE. The association between cigarette smoking and abdominal aortic aneurysms. J Vasc Surg 1999;30:1099–105.

23. Lange RA, Cigarroa RG, Yancy CW Jr., et al. Cocaine-induced coronary-artery vasoconstriction. N Engl J Med 1989;321:1557–62.

24. Rezkalla SH, Mazza JJ, Kloner RA, Tillema V, Chang SH. Effects of cocaine on human platelets in healthy subjects. Am J Cardiol 1993;72:243–6.

25. Siegel AJ, Mendelson JH, Sholar MB, et al. Effect of cocaine usage on C-reactive protein, von Willebrand factor, and fibrinogen. Am J Cardiol 2002;89:1133–5.

26. Moliterno DJ, Lange RA, Gerard RD, Willard JE, Lackner C, Hillis LD. Influence of intranasal cocaine on plasma constituents associated with endogenous thrombosis and thrombolysis. Am J Med 1994;96:492–6.

27. Kolodgie FD, Virmani R, Cornhill JF, Herderick EE, Smialek J. Increase in atherosclerosis and adventitial mast cells in cocaine abusers: an alternative mechanism of cocaine-associated coronary vasospasm and thrombosis. J Am Coll Cardiol 1991;17:1553–60.

28. Lucena J, Blanco M, Jurado C, et al. Cocaine-related sudden death: a prospective investigation in south-west Spain. Eur Heart J 2010;31:318–29.

29. Steinhauer JR, Caulfield JB. Spontaneous coronary artery dissection associated with cocaine use: a case report and brief review. Cardiovasc Pathol 2001;10:141–5.

30. Isner JM, Estes NA III, Thompson PD, et al. Acute cardiac events temporally related to cocaine abuse. N Engl J Med 1986;315:1438–43.

31. Remondino A, Kwon SH, Communal C, et al. β-Adrenergic receptor–stimulated apoptosis in cardiac myocytes is mediated by reactive oxygen species/c-Jun NH2-terminal kinase–dependent activation of the mitochondrial pathway. Circ Res 2003;92:136–8.

32. Nahas GG, Trouvé R, Manger WM. Cocaine, catecholamines and cardiac toxicity. Acta Anaesthesiol Scand Suppl 1990;94:77–81.

33. Billman GE, Hoskins RS. Cocaine-induced ventricular fibrillation: protection afforded by the calcium antagonist verapamil. FASEB J 1988;2:2990–5.

34. Shih RD, Hollander JE, Burstein JL, Nelson LS, Hoffman RS, Quick AM. Clinical safety of lidocaine in patients with cocaine-associated myocardial infarction. Ann Emerg Med 1995;26:702–6.

35. Ferreira S, Crumb WJ Jr., Carlton CG, Clarkson CW. Effects of cocaine and its major metabolites on the HERG-encoded potassium channel. J Pharmacol Exp Ther 2001;299:220–6.

36. O'Leary ME, Hancox JC. Role of voltage-gated sodium, potassium and calcium channels in the development of cocaine-associated cardiac arrhythmias. Br J Clin Pharmacol 2010;69:427–42.

37. Clarkson CW, Xu YQ, Chang C, Follmer CH. Analysis of the ionic basis for cocaine's biphasic effect on action potential duration in guinea-pig ventricular myocytes. J Mol Cell Cardiol 1996;28:667–78.

38. Crandall CG, Vongpatanasin W, Victor RG. Mechanism of cocaine-induced hyperthermia in humans. Ann Intern Med 2002;136:785–91.

39. Crumb WJ Jr., Clarkson CW. Characterization of cocaine-induced block of cardiac sodium channels. Biophys J 1990;57:589–99.

40. Hoffman RS. Treatment of patients with cocaine-induced arrhythmias: bringing the bench to the bedside. Br J Clin Pharmacol 2010;69:448–57.

41. El Mazloum R, Snenghi R, Zorzi A, et al. Out-of-hospital cardiac arrest after acute cocaine intoxication associated with Brugada ECG patterns: insights into physiopathologic mechanisms and implications for therapy. Int J Cardiol 2015;195:245–9.

42. Álvarez Díaz H, Mariño Callejo AI, García Rodríguez JF, Rodríguez Pazos L, Gómez Buela I, Bermejo Barrera AM. ANCA-positive vasculitis induced by levamisole-adulterated cocaine and nephrotic syndrome: the kidney as an unusual target. Am J Case Rep 2013;14:557–61.

43. Karch SB, Mari F, Bartolini V, Bertol E. Aminorex poisoning in cocaine abusers. Int J Cardiol 2012;158:344–6.

44. Albuquerque ML, Kurth CD. Cocaine constricts immature cerebral arterioles by a local anesthetic mechanism. Eur J Pharmacol 1993;249:215–20.

45. Volkow ND, Mullani N, Gould KL, Adler S, Krajewski K. Cerebral blood flow in chronic cocaine users: a study with positron emission tomography. Br J Psychiatry 1988;152:641–8.

46. Vongpatanasin W, Mansour Y, Chavoshan B, Arbique D, Victor RG. Cocaine stimulates the human cardiovascular system via a central mechanism of action. Circulation 1999;100:497–502.

47. Snyder SH. Nitric oxide: first in a new class of neurotransmitters. Science 1992;257:494–6.

48. Itzhak Y. Nitric oxide (NO) synthase inhibitors abolish cocaine-induced toxicity in mice. Neuropharmacology 1993;32:1069–70.

49. Fogo A, Superdock KR, Atkinson JB. Severe arteriosclerosis in the kidney of a cocaine addict. Am J Kidney Dis 1992;20:513–5.

50. Kibayashi K, Mastri AR, Hirsch CS. Cocaine induced intracerebral hemorrhage: analysis of predisposing factors and mechanisms causing hemorrhagic strokes. Hum Pathol 1995;26:659–63.

51. Brecklin CS, Gopaniuk-Folga A, Kravetz T, et al. Prevalence of hypertension in chronic cocaine users. Am J Hypertens 1998;11:1279–83.

52. Braun BL, Murray DM, Sidney S. Lifetime cocaine use and cardiovascular characteristics among young adults: the CARDIA study. Am J Public Health 1997;87:629–34.

53. Eagle KA, Isselbacher EM, DeSanctis RW, International Registry for Aortic Dissection (IRAD) Investigators. Cocaine-related aortic dissection in perspective. Circulation 2002;105:1529–30.

54. Hsue PY, Salinas CL, Bolger AF, Benowitz NL, Waters DD. Acute aortic dissection related to crack cocaine. Circulation 2002;105:1592–5.

55. Daniel JC, Huynh TT, Zhou W, et al. Acute aortic dissection associated with use of cocaine. J Vasc Surg 2007;46:427–33.

56. Dabbouseh NM, Ardelt A. Cocaine mediated apoptosis of vascular cells as a mechanism for carotid artery dissection leading to ischemic stroke. Med Hypotheses 2011;77:201–3.

57. Bigi MA, Aslani A, Mehrpour M. Effect of chronic cocaine abuse on the elastic properties of aorta. Echocardiography 2008;25:308–11.

58. Hall WC, Talbert RL, Ereshefsky L. Cocaine abuse and its treatment. Pharmacotherapy 1990;10:47–65.

59. Brody SL, Slovis CM, Wrenn KD. Cocaine-related medical problems: consecutive series of 233 patients. Am J Med 1990;88:325–31.

60. Mittleman MA, Mintzer D, Maclure M, Tofler GH, Sherwood JB, Muller JE. Triggering of myocardial infarction by cocaine. Circulation 1999;99:2737–41.

61. Weber JE, Shofer FS, Larkin GL, Kalaria AS, Hollander JE. Validation of a brief observation period for patients with cocaine-associated chest pain. N Engl J Med 2003;348:510–7.

62. Weber JE, Chudnofsky CR, Boczar M, Boyer EW, Wilkerson MD, Hollander JE. Cocaine-associated chest pain: how common is myocardial infarction? Acad Emerg Med 2000;7:873–7.

63. Gitter MJ, Goldsmith SR, Dunbar DN, Sharkey SW. Cocaine and chest pain: clinical features and outcome of patients hospitalized to rule out myocardial infarction. Ann Intern Med 1991;115:277–82.

64. Hollander JE, Levitt MA, Young GP, Briglia E, Wetli CV, Gawad Y. Effect of recent cocaine use on the specificity of cardiac markers for diagnosis of acute myocardial infarction. Am Heart J 1998;135:245–52.

65. Hollander JE, Hoffman RS, Gennis P, et al. Prospective multicenter evaluation of cocaine-associated chest pain. Cocaine Associated Chest Pain (COCHPA) Study Group. Acad Emerg Med 1994;1:330–9.

66. Rubin RB, Neugarten J. Cocaine-induced rhabdomyolysis masquerading as myocardial ischemia. Am J Med 1989;86:551–3.

67. Tashkin DP, Khalsa ME, Gorelick D, et al. Pulmonary status of habitual cocaine smokers. Am Rev Respir Dis 1992;145:92–100.

68. Hollander JE, Hoffman RS, Burstein JL, Shih RD, Thode HC Jr. Cocaine-associated myocardial infarction. Mortality and complications. Arch Intern Med 1995;155:1081–6.

69. Chase M, Brown AM, Robey JL, et al. Application of the TIMI risk score in ED patients with cocaine-associated chest pain. Am J Emerg Med 2007;25:1015–8.

70. Anderson JL, Adams CD, Antman EM, et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e179–348.

71. Kontos MC, Schmidt KL, Nicholson CS, Ornato JP, Jesse RL, Tatum JL. Myocardial perfusion imaging with technetium-99m sestamibi in patients with cocaine-associated chest pain. Ann Emerg Med 1999;33:639–45.

72. Walsh K, Chang AM, Perrone J, et al. Coronary computerized tomography angiography for rapid discharge of low-risk patients with

cocaine-associated chest pain. J Med Toxicol 2009;5:111–9.

73. Brogan WC III, Lange RA, Kim AS, Moliterno DJ, Hillis LD. Alleviation of cocaine-induced coronary vasoconstriction by nitroglycerin. J Am Coll Cardiol 1991;18:581–6.

74. Negus BH, Willard JE, Hillis LD, et al. Alleviation of cocaine-induced coronary vasoconstriction with intravenous verapamil. Am J Cardiol 1994;73:510–3.

75. Rappolt RT Sr., Gray GR, Inaba DS. Letter: Propranolol in the treatment of cardiopressor effect of cocaine. N Engl J Med 1976;295:448.

76. Rappolt RT, Gay GR, Inaba DS. Propranolol: a specific antagonist to cocaine. Clin Toxicol 1977;10:265–71.

77. Ramoska E, Sacchetti AD. Propranolol-induced hypertension in treatment of cocaine intoxication. Ann Emerg Med 1985;14:1112–3.

78. Catravas JD, Waters IW. Acute cocaine intoxication in the conscious dog: studies on the mechanism of lethality. J Pharmacol Exp Ther 1981;217:350–6.

79. Guinn MM, Bedford JA, Wilson MC. Antagonism of intravenous cocaine lethality in nonhuman primates. Clin Toxicol 1980;16:499–508.

80. Vargas R, Gillis RA, Ramwell PW. Propranolol promotes cocaine-induced spasm of porcine coronary artery. J Pharmacol Exp Ther 1991;257:644–6.

81. Lange RA, Cigarroa RG, Flores ED, et al. Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. Ann Intern Med 1990;112:897–903.

82. Boehrer JD, Moliterno DJ, Willard JE, Hillis LD, Lange RA. Influence of labetalol on cocaine-induced coronary vasoconstriction in humans. Am J Med 1993;94:608–10.

83. Fareed FN, Chan G, Hoffman RS. Death temporally related to the use of a beta adrenergic receptor antagonist in cocaine associated myocardial infarction. J Med Toxicol 2007;3:169–72.

84. McCord J, Jneid H, Hollander JE, et al. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. Circulation 2008;117:1897–907.

85. Rangel C, Shu RG, Lazar LD, Vittinghoff E, Hsue PY, Marcus GM. Beta-blockers for chest pain associated with recent cocaine use. Arch Intern Med 2010;170:874–9.

86. Ibrahim M, Maselli DJ, Hasan R. Safety of β-blockers in the acute management of cocaine-associated chest pain. Am J Emerg Med 2013;31:989.

87. Dattilo PB, Hailpern SM, Fearon K, Sohal D, Nordin C. β-Blockers are associated with reduced risk of myocardial infarction after cocaine use. Ann Emerg Med 2008;51:117–25.

88. Hoskins MH, Leleiko RM, Ramos JJ, Sola S, Caneer PM, Khan BV. Effects of labetalol on hemodynamic parameters and soluble biomarkers of inflammation in acute coronary syndrome in patients with active cocaine use. J Cardiovasc Pharmacol Ther 2010;15:47–52.

89. Sofuoglu M, Brown S, Babb DA, Pentel PR, Hatsukami DK. Effects of labetalol treatment on the physiological and subjective response to smoked cocaine. Pharmacol Biochem Behav 2000;65:255–9.

90. Sand IC, Brody SL, Wrenn KD, Slovis CM. Experience with esmolol for the treatment of cocaine-associated cardiovascular complications. Am J Emerg Med 1991;9:161–3.

91. McKee SA, Applegate RJ, Hoyle JR, Sacrinty MT, Kutcher MA, Sane DC. Cocaine use is associated with an increased risk of stent thrombosis after percutaneous coronary intervention. Am Heart J 2007;154:159–64.

92. Mongeon FP, Rinfret S. Left main coronary artery occlusion with myocardial infarction in a cocaine user. Successful angioplasty with a drug-eluting stent. Can J Cardiol 2008;24:e30–2.

93. Shah P, Vasudev R, Abuarqoub AH, Shamoon F. Cocaine-induced very late stent thrombosis. BMJ Case Rep 2016;2016.

94. Price FW, Leakey AB. Grave and prolonged cardiac failure following the use of cocaine in dental surgery. Lancet 1911;177:797–8.

95. Hale SL, Alker KJ, Rezkalla S, Figures G, Kloner RA. Adverse effects of cocaine on cardiovascular dynamics, myocardial blood flow, and coronary artery diameter in an experimental model. Am Heart J 1989;118:927–33.

96. Pitts WR, Vongpatanasin W, Cigarroa JE, Hillis LD, Lange RA. Effects of the intracoronary infusion of cocaine on left ventricular systolic and diastolic function in humans. Circulation 1998;97:1270–3.

97. Hoffman CK, Goodman PC. Pulmonary edema in cocaine smokers. Radiology 1989;172:463–5.

98. Bertolet BD, Freund G, Martin CA, Perchalski DL, Williams CM, Pepine CJ. Unrecognized left ventricular dysfunction in an apparently healthy cocaine abuse population. Clin Cardiol 1990;13:323–8.

99. Om A, Warner M, Sabri N, Cecich L, Vetrovec G. Frequency of coronary artery disease and left ventricle dysfunction in cocaine users. Am J Cardiol 1992;69:1549–52.

100. Arora S, Alfayoumi F, Srinivasan V. Transient left ventricular apical ballooning after cocaine use: is catecholamine cardiotoxicity the pathologic link? Mayo Clin Proc 2006;81:829–32.

101. Perreault CL, Hague NL, Ransil BJ, Morgan JP. The effects of cocaine on intracellular $Ca2+$ handling and myofilament $Ca2+$ responsiveness of ferret ventricular myocardium. Br J Pharmacol 1990;101:679–85.

102. Schulze JJ, Knops J. Effects of flecainide on contractile force and electrophysiological parameters in cardiac muscle. Arzneimittelforschung 1982;32:1025–9.

103. Isabelle M, Monteil C, Moritz F, et al. Role of α1-adrenoreceptors in cocaine-induced NADPH oxidase expression and cardiac dysfunction. Cardiovasc Res 2005;67:699–704.

104. Frustaci A, Russo MA, Morgante E, et al. Oxidative myocardial damage in human cocaine-related cardiomyopathy. Eur J Heart Fail 2015;17:283–90.

105. Mosunjac MI, Sundstrom JB, Heninger M, Ansari AA, Mosunjac MB. Combined pathological effects of cocaine abuse and HIV infection on the cardiovascular system: an autopsy study of 187 cases from the Fulton County Medical Examiner's office. Am J Forensic Med Pathol 2008;29:9–13.

106. Virmani R, Robinowitz M, Smialek JE, Smyth DF. Cardiovascular effects of cocaine: an autopsy study of 40 patients. Am Heart J 1988;115:1068–76.

107. Gradman AH. Cardiac effects of cocaine: a review. Yale J Biol Med 1988;61:137–47.

108. Bauman JL, Grawe JJ, Winecoff AP, Hariman RJ. Cocaine-related sudden cardiac death: a hypothesis correlating basic science and clinical observations. J Clin Pharmacol 1994;34:902–11.

109. Shen MJ, Choi EK, Tan AY, et al. Neural mechanisms of atrial arrhythmias. Nat Rev Cardiol 2011;9:30–9.

110. Friedman RA, Kearney DL, Moak JP, Fenrich AL, Perry JC. Persistence of ventricular arrhythmia after resolution of occult myocarditis in children and young adults. J Am Coll Cardiol 1994;24:780–3.

111. Wang RY. pH-dependent cocaine-induced cardiotoxicity. Am J Emerg Med 1999;17:364–9.

112. Winecoff AP, Hariman RJ, Grawe JJ, Wang Y, Bauman JL. Reversal of the electrocardiographic effects of cocaine by lidocaine. Part 1. Comparison with sodium bicarbonate and quinidine. Pharmacotherapy 1994;14:698–703.

113. Xu YQ, Crumb WJ Jr., Clarkson CW. Cocaethylene, a metabolite of cocaine and ethanol, is a potent blocker of cardiac sodium channels. J Pharmacol Exp Ther 1994;271:319–25.

114. O'Leary ME. Inhibition of HERG potassium channels by cocaethylene: a metabolite of cocaine and ethanol. Cardiovasc Res 2002;53:59–67.

115. Krantz MJ, Rowan SB, Mehler PS. Cocaine-related torsade de pointes in a methadone maintenance patient. J Addict Dis 2005;24:53–60.

116. Kimura S, Bassett AL, Xi H, Myerburg RJ. Early afterdepolarizations and triggered activity induced by cocaine. A possible mechanism of cocaine arrhythmogenesis. Circulation 1992;85:2227–35.

117. Kosten TR, Kleber HD. Rapid death during cocaine abuse: a variant of the neuroleptic malignant syndrome? Am J Drug Alcohol Abuse 1988;14:335–46.

118. Marzuk PM, Tardiff K, Leon AC, et al. Ambient temperature and mortality from unintentional cocaine overdose. JAMA 1998;279:1795–800.

119. Akhtar MJ, al-Nozha M, al-Harthi S, Nouh MS. Electrocardiographic abnormalities in patients with heat stroke. Chest 1993;104:411–4.

120. Beckman KJ, Parker RB, Hariman RJ, Gallastegui JL, Javaid JI, Bauman JL. Hemodynamic and electrophysiological actions of cocaine. Effects of sodium bicarbonate as an antidote in dogs. Circulation 1991;83:1799–807.

121. Grawe JJ, Hariman RJ, Winecoff AP, Fischer JH, Bauman JL. Reversal of the electrocardiographic effects of cocaine by lidocaine. Part 2. Concentration-effect relationships. Pharmacotherapy 1994;14:704–11.

122. DeWitt CR, Cleveland N, Dart RC, Heard K. The effect of amiodarone pretreatment on survival of mice with cocaine toxicity. J Med Toxicol 2005;1:11–8.

123. Weinberg G, Ripper R, Feinstein DL, Hoffman W. Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity. Reg Anesth Pain Med 2003;28:198–202.

124. Arora NP, Berk WA, Aaron CK, Williams KA. Usefulness of intravenous lipid emulsion for cardiac toxicity from cocaine overdose. Am J Cardiol 2013;111:445–7.

125. Lavonas EJ, Drennan IR, Gabrielli A, et al. Part 10: Special circumstances of resuscitation: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132:S501–18.

126. Chin KM, Channick RN, Rubin LJ. Is methamphetamine use associated with idiopathic pulmonary arterial hypertension? Chest 2006;130:1657–63.

127. Kleerup EC, Wong M, Marques-Magallanes JA, Goldman MD, Tashkin DP. Acute effects of intravenous cocaine on pulmonary artery pressure and cardiac index in habitual crack smokers. Chest 1997;111:30–5.

128. Schaiberger PH, Kennedy TC, Miller FC, Gal J, Petty TL. Pulmonary hypertension associated with long-term inhalation of "crank" methamphetamine. Chest 1993;104:614–6.

129. Andrews CM, Lucki I. Effects of cocaine on extracellular dopamine and serotonin levels in the nucleus accumbens. Psychopharmacology (Berl) 2001;155:221–9.

130. Ducas J, Duval D, Dasilva H, Boiteau P, Prewitt RM. Treatment of canine pulmonary hypertension: effects of norepinephrine and isoproterenol on pulmonary vascular pressure-flow characteristics. Circulation 1987;75:235–42.

131. Harrison DC, Pirages S, Robison SC, Wintroub BU. The pulmonary and systemic circulatory response to dopamine infusion. Br J Pharmacol 1969;37:618–26.

132. Daggett RB, Haghighi P, Terkeltaub RA. Nasal cocaine abuse causing an aggressive midline intranasal and pharyngeal destructive process mimicking midline reticulosis and limited Wegener's granulomatosis. J Rheumatol 1990;17:838–40.

133. Trimarchi M, Gregorini G, Facchetti F, et al. Cocaine-induced midline destructive lesions: clinical, radiographic, histopathologic, and serologic features and their differentiation from Wegener granulomatosis. Medicine (Baltimore) 2001;80:391–404.

134. McGrath MM, Isakova T, Rennke HG, Mottola AM, Laliberte KA, Niles JL. Contaminated cocaine and antineutrophil cytoplasmic antibody-associated disease. Clin J Am Soc Nephrol 2011;6:2799–805.

135. Toossi S, Hess CP, Hills NK, Josephson SA. Neurovascular complications of cocaine use at a tertiary stroke center. J Stroke Cerebrovasc Dis 2010;19:273–8.

136. Kalani R, Liotta EM, Prabhakaran S. Diagnostic yield of universal urine toxicology screening in an unselected cohort of stroke patients. PLoS One 2015;10:e0144772.

137. Westover AN, McBride S, Haley RW. Stroke in young adults who abuse amphetamines or cocaine: a population-based study of hospitalized patients. Arch Gen Psychiatry 2007;64:495–502.

138. Cheng YC, Ryan KA, Qadwai SA, et al. Cocaine use and risk of ischemic stroke in young adults. Stroke 2016;47:918–22.

139. Qureshi AI, Akbar MS, Czander E, Safdar K, Janssen RS, Frankel MR. Crack cocaine use and stroke in young patients. Neurology 1997;48:341–5.

140. Jauch EC, Saver JL, Adams HP Jr., et al., American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870–947.

141. Hemphill JC III, Greenberg SM, Anderson CS, et al., American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Clinical Cardiology. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015;46:2032–60.

142. Martin-Schild S, Albright KC, Hallevi H, et al. Intracerebral hemorrhage in cocaine users. Stroke 2010;41:680–4.

143. Martin-Schild S, Albright KC, Misra V, et al. Intravenous tissue plasminogen activator in patients with cocaine-associated acute ischemic stroke. Stroke 2009;40:3635–7.

144. Roberts DC, Morgan D, Liu Y. How to make a rat addicted to cocaine. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:1614–24.

145. Nestler EJ. The neurobiology of cocaine addiction. Sci Pract Perspect 2005;3:4–10.

146. Fischbach P. The role of illicit drug use in sudden death in the young. Cardiol Young 2017;27:S75–9.

KEY WORDS acute myocardial infarction, beta-blockers, cardiomyopathy, cocaine cardiotoxicity, drug addiction