Cocaine and the critical care challenge

Christina M. Shanti, MD; Charles E. Lucas, MD, FCCM

Objective: **Cocaine, which first made its appearance >1,000 yrs ago, is now widely used throughout the world. The physiologic responses to cocaine may cause severe pathologic effects. This review highlights the many critical care challenges resulting from these effects.**

Design: **Historical vignettes, epidemiologic factors, modes of preparation and delivery, and the physiologic and pharmacologic effects of these agents are presented.**

Setting: **Cocaine causes intense vasoconstriction, which potentially causes damage to all organ systems. Examples of these toxicities are presented.**

Patients: **The adverse multisystem responses to cocaine exposure produce organ failure, which challenges diagnostic accuracy and therapeutic intervention. Organ system failure involves the brain, heart, lung, kidneys, gastrointestinal tract, musculature, and other organs. These harmful effects are additive to preexisting organ dysfunction.**

Intervention: **Recognition of associated cocaine injury alerts the physician that organ dysfunction is more likely to occur and to be more severe. Such anticipation helps plan for therapy in the critical care setting.**

Results and Conclusions: **Cocaine use is an expanding health hazard, despite intense governmental efforts to contain its distribution and use. Recognition of the signs and symptoms of cocaine toxicity help anticipate the subsequent organ dysfunction and implement earlier organ system support. (Crit Care Med 2003; 31:1851–1859)**

Key Words: cocaine; critical care; organ failure

Cocaine has become a major confounder in the diagnosis and treatment of surgical emergencies. This complex drug made its first appearance about 1200 yrs ago in the northern Andes of Peru and Bolivia. Figures depicted on ceramic pottery show that coca leaves were harvested and chewed by the Indians (1–3). Anthropologic studies reveal that cocaine-filled saliva of the chewed coca leaves was used as a local anesthetic during trephining operations for traumatic intracranial hematomas (1). The Incas founded their capital at Cuzco, Peru, in 1021 AD, and their empire flourished (2). They believed in a supreme being represented by the sun, worshipped that which gave life, including the coca plant, named their first queen "Mama Cuca," and placed the coca leaf on the royal emblem (1, 2). Consumption of the "divine" coca leaf was reserved for priests during religious ceremonies, the sovereign Inca, and occasionally soldiers (2). The coca leaves were also given by the Inca as a reward or token of appreciation (1). Coca leaf storehouses were built along the roads to supply messengers who carried messages at a rate of 150 miles a day (2). The word cocada is a measure of the distance a man can walk without tiring under the influence of the coca leaf. When Pizarro conquered the Incan Empire in 1533, the Indian slaves working in Spanish silver mines chewed the coca leaf to fight fatigue and hunger (1, 3). The Spanish capitalized on this practice by enforcing a 5% tax on the coca crop. The church received its share of the tax money and supported this practice (2). The Spaniard Nicolas Monardes wrote the first scientific article on coca in 1565 (1, 2, 4). Later, in 1580, he brought coca leaves to Europe (1, 2). Coca use in Europe flourished during the next 300 yrs, and many publications appeared (1, 4). In 1854, the United States sent its first investigational expedition to South America. Pizzi, a laboratory director at LaPaz in Bolivia, extracted the alkaloid (2). In 1857, Gaedicke extracted a sublimate of small crystals he named erythroxyline (1, 2). In 1860, Niemann isolated the alkaloid from the coca leaves and named it cocaine (1, 2, 4). In 1862, Schroff and Demarle observed that cocaine produced analgesia of the tongue and, subsequently, its use in relieving laryngeal pain became popular in England and America (2).

During the 1880s Freud experimented with cocaine and used it to treat opiate addiction (1, 2, 4, 5). Several of his articles describe its powerful effects and advocate its use for increasing physical capacity, treating digestive disorders and cachexia, counteracting morphine and alcohol withdrawal, treating asthma, and stimulating sexual activity. The strong euphoriant properties of cocaine contributed to Freud's transient addiction. Interestingly, Freud's experimentation with cocaine preceded his work in psychoanalysis and hypnosis. This period of cocaine use was eliminated from his autobiography (1). Concomitantly, Freud's friend Carl Koller, a Viennese ophthalmologist, conducted animal and clinical experiments that corroborated his theory that cocaine can produce anesthesia in the cornea and conjunctiva, thus introducing cocaine as a local anesthetic for ophthalmologic procedures (1–3, 6).

The North American medical experiences with cocaine date to Halstead who performed the first nerve block using injectable cocaine; by 1886, he was battling his own addiction to cocaine, which reportedly reached 2 g/day (1, 3, 6). George Crile in 1897 used direct nerve infiltration of cocaine in amputation. Cushing

From the Department of Surgery, The Detroit Medical Center/Wayne State University School of Medicine, Detroit, MI.

Supported, in part, by an Interstitial Fluid Fund, account 4-44966.

Address requests for reprints to: Charles E. Lucas, MD, Department of Surgery, Wayne State University, 4201 St. Antoine, Room 2V, Detroit, MI 48201. E-mail: clucas@med.wayne.edu

DOI: 10.1097/01.CCM.0000063258.68159.71

performed the first herniorrhaphy using cocaine-induced nerve block. By 1898 cocaine became widely used by several physicians to induce spinal anesthesia (1). Sir Arthur Conan Doyle described his own addiction through Sherlock Holmes who, from 1888 until 1891, was tireless with cocaine his weapon. Holmes became increasingly paranoid and withdrawn, and he disappeared at Reichenbach Falls in 1891 (1, 4). When he reappeared in 1894 a pipe had replaced the cocaine addiction, and his health was restored (4).

The Age of the Cocainized Nostrum began in the 1890s and ended in 1914 (1). Pemberton, a Georgia pharmacist, compounded the Coca-Cola syrup in 1886. This was a combination of the coca leaf cocaine extract and the African kola nut caffeine extract. Pemberton sold 25 gallons of his syrup for $50 and used 90% of his profits for advertisement (5). Candler bought Coca-Cola and introduced the soft drink in 1892 as a tonic for the elderly people who were easily tired. Cocaine was sold in cigarettes, cigars, inhalants, coca liquors, crystals, solution form, and wine (1, 5). Cocaine was promoted for the treatment of opiate and alcohol addiction, runny nose, sore throat, headaches, fatigue, hay fever, high blood pressure, nervous disorders, and even tuberculosis (5).

Soon, nonmedical cocaine use and abuse increased. By 1902, Crother reported that only 5% of the cocaine sold in New York and other metropolitan areas was used for medicine and dentistry (1). Medical experts issued notes of caution on cocaine use, and the public critical attitude toward cocaine, in 1903, caused the manufacturer to voluntarily remove cocaine from the Coca-Cola drink (5). The Coca-Cola company today still extracts cocaine from imported leaves but turns it over to the government for medical use. Processed leaves are still used as a flavoring agent (3).

In 1913, President Taft pronounced cocaine to be "public enemy #1," and, in 1914, Congress passed the Harrison "Narcotics" Tax Act, which required persons authorized to handle and manufacture drugs to keep a record of all "narcotics" (including cocaine) in their possession (1, 6, 7). This mislabeled cocaine as a narcotic and drove it underground (1). Nationwide, educational efforts were launched, and by the 1950s, recreational use was minimal, whereas its use in medical practice particularly as a topical anesthetic, decongestant, and vasoconstrictor for intranasal procedures continued (1, 6). The past generation has seen a new upsurge in the popularity and use of cocaine partly due to the widespread availability of inexpensive crack cocaine (1, 7).

EPIDEMIOLOGY

Cocaine abuse and dependence is epidemic in the United States. More than 50 million Americans have used cocaine, and >6 million Americans of all ages use it on a regular basis. The national prevalence of cocaine use is highest among 18- to 25-yr olds but is becoming quite popular in the teenage group. The reported use is 3% of 12- to 17-yr olds including about 1% who use it daily (8). In New York City between 1990 and 1992, 26.7% of fatal injury victims had cocaine metabolites in their urine or blood. More than 30% of deaths after cocaine use were the result of drug intoxication; 65% involved traumatic injuries from homicide, suicide, traffic accidents, and falls. Death after cocaine use is one of the five leading causes of death in the 15- to 44-yr-old age group (9). More than 20% of patients with orthopedic injuries in an inner city environment test positive for cocaine. This is often associated with more severe injuries requiring a longer length of stay (10). About 20% of blunt trauma patients and 57% of penetrating trauma patients test positive for cocaine (11). In a study of 42,981 patients admitted to R. Adams Cowley Shock Trauma Center in Maryland between July 1984 and December 1998, there was a 262% increase in cocaine use in all victims of violence and a 161% increase in victims of nonviolent injuries (12).

The cocaine supply industry is growing. In Columbia, the coca fields have expanded from 100,000 acres in 1994 to 250,000 acres in 1998. According to United Nations figures, coca production has doubled since 1985, and the drug prices are falling (13). The war against drugs has become increasingly more costly during the past two decades. The federal government drug budget has grown from $1.5 billion in 1981 to $14 billion in 1995, and the epidemic continues to grow (8, 13).

COCAINE PREPARATION

From Leaf to Powder. Cocaine is an alkaloid of the *Erythroxylin* coca bush, a shrub grown in the Andes mountains in western South America with Peru, Columbia, Ecuador, and Bolivia being the main producing countries (1, 3, 8). Cocaine in the United States has traditionally come mostly from Columbia and Peru, although more and more is coming from Asia (8). The coca bush may grow to 8 feet with leaves twice the size of a thumbnail. Cocaine can be produced within 18 months of planting and throughout a 40-yr lifespan. The leaves are harvested in the months of March, June, and November. They are placed in gasoline drums with kerosene and other solvents. The mixture is allowed to soak, then the fluid is drawn off, and the leaves are removed. The remaining thick paste is placed in containers and sold to "laboratory agents." The laboratories refine the paste into the cocaine powder (1). Coca leaves yield approximately 0.65% to 1.2% of their weight in cocaine (1, 3). Cocaine, or benzoylmethylecgonine, is treated with hydrochloric acid to form the cocaine hydrochloride salt, which is freely soluble in water and can be injected intravenously or absorbed through the nasal mucosa (1, 8). Freebase and crack cocaine are prepared from the same cocaine alkaloid form using two different techniques (8).

Freebase. Cocaine hydrochloride is dissolved in water, and ammonia is added as a base. The cocaine base is then dissolved in ether and is extracted by evaporating the ether at low temperature. The cocaine freebase can then be smoked, mixed with tobacco, or inhaled by heating it in special pipes. Occasionally, traces of the highly volatile ether remain after the extraction process, and this may ignite, causing ether burns particularly of the face and trachea (8).

Crack Cocaine. Cocaine hydrochloride is dissolved in water, then mixed with baking soda. The mixture is heated, and the cocaine base precipitates into a soft mass that dries into a hard "rock." Crack cocaine may be smoked using a glass or regular pipe or by mixing it with tobacco or marijuana. The name crack comes from the "popping" sound the cocaine crystals make when smoked. Crack is inexpensive and readily available; it is currently the most popular form being used by most cocaine addicts (8).

Cocaine is also known as Snow, Flake, Her, Girl, Lady, Blow, She, Jam, Happy Trails, Rock, Nose-candy, The Star Spangled Powder, Dama Blanca, The gift of the Sun God, Heaven Leaf, The Rich Man's Drug, Speedball Coke, Gold Dust, Bernice, and The Pimp's Drug (1, 8). A "speedball" is a combination of cocaine

and heroin taken intravenously, presumably doubling the "rush" (1, 3). Patients on methadone often turn to cocaine for a kick because its euphoriant effects are not altered by methadone (3).

PHARMACOLOGY AND PHARMACOKINETICS

Cocaine is benzoylmethylecgonine, an ester of benzoic acid and the nitrogen-containing base ecgonine; ecgonine is a tropine derivative and is the parent compound of atropine and scopolamine. Cocaine is the only naturally occurring local anesthetic (1). Because it is absorbed through any mucous membrane, cocaine can be inhaled, snorted, or injected intravenously or intramuscularly (14). The half-life is 30–90 mins. Smoked crack cocaine is absorbed through the pulmonary vasculature and reaches the cerebral circulation in 6–8 secs, producing intense euphoria. Intravenous cocaine takes about 12–16 secs to reach the brain. Snorted cocaine, on the other hand, requires 3–5 mins to reach the brain. Intranasal cocaine causes local vasoconstriction, thus limiting quick absorption; its plasma concentration peaks at 60 mins and persists for up to 6 hrs. This explains why snorted cocaine yields the most prolonged euphoria (8).

The highest organ concentrations of cocaine appear in the brain, spleen, kidney, and lungs. About 80% to 90% of cocaine is metabolized to a) ecgonine methyl esters by rapid enzymatic hydrolysis by plasma and liver esterases; b) benzoylecgonine by spontaneous nonenzymatic hydrolysis; and c) norcocaine by liver N-demethylation. Between 1% and 5% remains unaltered and is excreted in the urine 3 to 6 hrs after use. Cocaine metabolites can be detected in the urine for 6 to 14 days after administration. When taken in proximity to ethanol ingestion, cocaine is transesterified by a liver esterase to ethylcocaine, which potentiates cocaine's systemic toxicity (8, 14).

Cocaine blocks the reuptake of catecholamines by the presynaptic sympathetic nerve terminals, resulting in accumulation of catecholamines in the synaptic clefts and increasing cell receptor stimulation. Cocaine exerts its local anesthetic effects by blocking fast sodium channels in neuronal cells and impairing conduction of nerve impulses (14). In the cardiac myocyte, it decreases the rate of depolarization and amplitude of the action potential and can slow the conduction rate of the action potential; this may cause cardiac dysrhythmias and sudden death (8, 14). In the mesolimbic and mesocortical areas of the brain, cocaine blocks the dopamine uptake pump and impairs dopamine reuptake into the presynaptic neurons, which results in dopamine accumulation in the synaptic cleft and sustained stimulation of dopaminergic receptors; this produces intense euphoria with increased alertness and self-confidence (8, 14, 15). Concomitant suppression of the activity of the pontine nucleus and the locus ceruleus suppresses feelings of fear and panic (8, 14). The craving for cocaine comes from depletion of dopaminergic stores in the presynaptic neurons after repetitive use (15). This causes an increase in the number of the presynaptic dopaminergic receptors, which require larger and larger doses of cocaine to produce the same euphoric effect. This tachyphilactic phenomenon within the central nervous system is only partially seen in the cardiovascular system, resulting in the catastrophic cardiovascular events often seen during a cocaine binge (8). Cocaine also blocks presynaptic serotonin binding sites and inhibits serotonin reuptake and removal. The consequent serotonin accumulation in the brain causes intense stimulation and may precipitate seizures. Intense central nervous system stimulation is also achieved by direct cocaine binding to sigma and muscarinic (M1 and possibly M2) receptors (14). In high concentrations, cocaine can act as an anticholinergic drug through muscarinic receptor blockade, resulting in decreased gastric motility and subsequent ulceration secondary to prolonged acid exposure (8, 15).

In the lungs, cocaine impairs alveolar macrophage function and cytokine production, which may result in local immunosuppression and infectious complications (16). It also activates polymorphonuclear cells, resulting in a burst of acute inflammatory activity that may contribute to further lung injury (17). Cocaine also increases platelet activation and aggregation, decreases protein C and antithrombin III levels, and increases plasminogen activator inhibitor activity. This induces a prothrombotic effect in both small and large blood vessels (18–20). Animal studies show that cocaine, in a dose-dependent fashion, affects the heat regulation center in the hypothalamus and causes significant alterations in the core temperature (21–23).

TOXICOLOGICAL SCREENING

Screening for cocaine and its metabolites can be performed on many biological fluids and tissues including urine, serum, saliva, gastric aspirates, breast milk, meconium, and even hair (24–26). In the acute setting, urine testing is widely used and is least expensive. Two methods are generally employed. The first is an immunoassay *qualitative* method for cocaine's most common metabolite, benzoylecgonine. Depending on the concentration cutoff set by the lab, this test can be 94% to 100% specific. The lower the concentration cutoff (lowest is 150 ng/mL), the higher the sensitivity and specificity. The immunoassay test can be confirmed if desired by a *quantitative* gas chromatography-mass spectrometry method. This is substantially more expensive($200.00 vs. $0.10) and is done only when specifically requested. In general, urine testing will remain positive up to 6–14 days, but the results of both tests, however, depend on the amount of cocaine used, the time it was used last, and the patient's renal function. Test results should, therefore, be interpreted while taking the above into consideration (27–29).

PATHOPHYSIOLOGY

Cocaine exposure produces a myriad of signs and symptoms, which obscure the classic response to injury and hemorrhagic shock. Acute cocaine exposure in high doses may be associated with hyperthermia, hypertension, tachycardia, mydriasis, seizures, stupor, and respiratory and cardiac depression. Death can occur within 2–3 mins, and attention should be paid to securing the airway, assuring breathing, and close cardiac monitoring. Beta blockade may be needed to control the acute sympathomimetic effects, whereas barbiturates are generally used for management of convulsions. Benzodiazepines can be used for anxiety as well as the treatment of hypertension (14). The treatment of these systemic effects of acute cocaine exposure is often complicated by more life-threatening organ-specific toxicities.

Central Nervous System Complications. Perhaps the most devastating central nervous system complication of cocaine is a stroke. The stroke can be ischemic secondary to cocaine-related vasospasm, or cerebral artery thrombosis or, rarely, cerebral vasculitis (30–33). A stroke can also be hemorrhagic second-

ary to a cocaine-induced hypertensive crisis resulting in ruptured berry aneurysms or arteriovenous malformations (34, 35). A patient with severe injury and hypovolemia due to hemorrhage may exhibit a normal mean arterial pressure due to pathologic vasoconstriction; this combination promotes added cerebral insult, which may not be fully appreciated by the resuscitation team. Cocaine can also precipitate generalized tonic and clonic convulsions and focal seizures. These are usually secondary to intense central nervous system stimulation either directly by cocaine on the sigma and muscarinic receptors or indirectly by the increase in serotonin central nervous system levels. Patients who are seizure prone have a lower seizure threshold with cocaine exposure (36). Seizures can also result from the acute hyperthermia due to cocaine-induced increased muscular activity and intense vasoconstriction, which impairs heat dissipation (8). Cocaine-induced seizures may complicate the initial resuscitation of an injured patient and may compromise the establishment of an airway and institution of intravenous catheters. Repetitive small doses of cocaine cause subthreshold stimulation of the limbic system and ultimately precipitate a seizure; a phenomenon known as kindling (36).

Cocaine-related accumulation of dopamine in the basal ganglia can cause a variety of movement disorders, namely Tourette's syndrome, tardive dyskinesia, choreoathetosis, akathisia, and dystonic reactions. In fact, cocaine users with chorea and akathisia are known as "crack dancers" (8). Manifestations of these behaviors after operative treatment of an emergency surgical problem may be confused with therapeutic drug reactions, electrolyte abnormalities, psychological aberrations, or even unusual manifestations of sepsis. Recently, a 53-yr-old cocaine-using woman presented 3 days after a 20% total body scald burn with confusion and sepsis. She developed excessive urine output, which was attributed to the inappropriate polyuria of sepsis, when, in fact, the patient had suffered from a cocaine-induced stroke 3 yrs earlier that led to diabetes insipidus. Her confusion was not due to sepsis, as originally thought, but was a result of her cocaine-induced stroke.

Pulmonary Complications. Pulmonary complications secondary to cocaine use occur in 25% of users and extend from simple asthma to fatal pulmonary hemorrhage (37). The frequency of pulmonary infarction is not known. These conditions present a special threat to the cocaine user and may compound the respiratory compromise due to injury or sepsis. Both upper and lower respiratory tract complications are common. Habitual snorters can present with epistaxis, nasal septal perforations, and oropharyngeal ulcers due to vasoconstriction and consequent ischemic necrosis (38). Preseptal cellulitis, palatal necrosis, and osteolytic sinusitis have also been reported (39–41). Inhalation of hot cocaine vapors and spontaneous ignition of residual ether in freebase cocaine cause thermal burns of the face and upper airway, leading to both acute inflammation of the tongue, epiglottis, vocal cords, and trachea and result in subsequent chronic scarring. As a direct airway irritant, cocaine damages bronchial epithelial cells, exposes and stimulates vagal receptors, and causes severe bronchospasm, thus exacerbating asthma (42–44). Patients present with wheezing, hoarseness, coughing, carbonaceous sputum, and singed nasal hairs (37, 38, 42). Expectoration of black sputum results from the inhalation of the carbonaceous residue from butane- or alcohol-soaked cotton sponges used to ignite the cocaine (42).

Cocaine also acts as an antigen and induces immunoglobulin-E production. This reaction occurs on the surface of mast cells after reexposure to cocaine and causes the release of histamine, serotonin, and eosinophil chemotactic factor, which causes direct lung injury (8). Cocaine also acts as a hapten and, combined with albumin or globulin, induces hypersensitivity pneumonitis (also known as *crack lung*), which is characterized by fever, dyspnea, wheezing, and productive cough associated with diffuse interstitial and alveolar infiltrates. Less commonly, cocaine causes bronchiolitis obliterans (42). Pulmonary granulomas and pneumoconiosis-like reactions may be occasionally found in cocaine users due to inhalation of talc, cellulose, or silica, which are often mixed with cocaine (38).

Regardless of route of administration, cocaine causes both pulmonary and bronchial arterial constriction and ischemia leading to interstitial and alveolar hemorrhage (37, 38). Inhaled impurities can cause injury directly to the alveolar epithelium and pulmonary basement membrane. Up to 25% of cocaine smokers present with hemoptysis secondary to pulmonary hemorrhage. Pulmonary infarction is seen less commonly because of the dual blood supply, but occasionally the severe vascular spasm and arterial endothelial injury with cocaine binging may result in platelet aggregation and pulmonary infarction (8, 42).

Cocaine's direct endothelial toxicity causes increased permeability and noncardiogenic pulmonary edema (37, 42). Cocaine can also cause markedly increased vascular resistance and acute left ventricular failure, which results in cardiogenic pulmonary edema (8). These pulmonary changes appear to be additive to those seen with hemorrhagic shock and sepsis. Patients with moderate insults may undergo successful treatment only to succumb to progressive cardiopulmonary dysfunction. Chronic cocaine use may result in pulmonary artery hypertension and hypertrophy leading to cor pulmonale, a complication that is independent of the dose, frequency, or route of cocaine administration (45, 46).

Pneumomediastinum, pneumopericardium, and pneumothorax can occur in cocaine smokers who take deep prolonged inspirations followed by a Valsalva maneuver to increase absorption and intensify central nervous system stimulation and euphoria. Absorption of cocaine is also enhanced by positive-pressure ventilation applied through direct mouth-to-mouth contact with another person. These maneuvers cause an acute elevation in airway pressure, which predisposes to alveolar rupture. Free air dissects into the mediastinum, neck, pericardium, and pleura (11, 37, 38, 47). A "Hamman crunch" can be heard upon auscultation of the precordium during systole (11, 47). Substernal chest pain is often present (11, 28). These entities may not always require tube thoracostomy because they resolve spontaneously (37, 38, 42). Treatment is supportive during the subsequent period of observation (38, 47). Rarely does the air dissect centrally in both the arterial and venous systems. Venous air may pass through the left heart and cause diffuse embolization and organ failure. Symptoms may include temporary visual disturbances, confusion or convulsions from cerebral air embolization, renal insufficiency, and myocardial infarction from coronary artery air embolization (11).

Cardiac Complications. A wide range of cardiac complications result from both acute and chronic cocaine use. Acute myocardial infarction may occur in patients with normal or diseased coronary

arteries, and both Q-wave and non-Q-wave changes may be seen on the electrocardiogram (8). The pathophysiology of myocardial infarction is multifactorial. Cocaine increases the heart rate, blood pressure, and systemic vascular resistance by blocking the reuptake of norepinephrine in the sympathetic nerve terminals throughout the cardiovascular system. Beta- and alpha-adrenergic receptor stimulation increases calcium concentration in the cardiac myocyte, which causes increased calcium uptake by the troponin-actin-myosin contractile complex. The increase in heart rate and blood pressure as well as cardiac contractility increase cardiac oxygen demand, which exceeds the oxygen supply provided by coronary arteries in vasospasm. Infarction can also result from focal coronary artery or diffuse spasm in patients with coronary atherosclerosis. Patients with coronary artery disease have impaired release of nitric oxide and prostacyclin from the endothelial cells and, consequently, impaired coronary endothelial-mediated vasodilatation. This exacerbates the vasoconstrictive effects of cocaine. Chronic cocaine use also accelerates coronary atherosclerotic disease as seen at autopsy in up to 40% of young cocaine users who die of acute myocardial infarction. Cocaine can also cause direct endothelial injury, which causes platelet aggregation, thromboxane production, and coronary artery thrombosis as yet another mechanism for myocardial infarction (48–50). Cocaine can cause acute myocarditis, which may be confused with myocardial infarction (48, 49). Therefore, a hypovolemic or septic patient with cocaine intoxication can present with significant cardiac demand and a low-flow-state condition, which can result in death.

The cocaine-induced cardiac arrhythmias, namely ventricular tachycardia and fibrillation, lead to sudden death. This is secondary to increased circulating norepinephrine and myocardial intracellular calcium. Cocaine can also block fast sodium channels, which impairs propagation of an electric impulse and results in conduction block and reentrant arrhythmias.

Cocaine induces ventricular hypertrophy and dilation and subsequent depression of left ventricular contractility and relaxation in up to 50% of chronic cocaine users. This is associated with dilated cardiomyopathy from hypertension, direct toxic effects of high concentrations of norepinephrine or myocardial stunning secondary to coronary vasospasm, and transient cessation of blood flow. The cardiac dilation is reversible if circulating catecholamine levels are promptly normalized. Chronic cocaine use, however, results in persistently high concentrations of catecholamines, which causes myocytolysis and fibrosis and subsequent chronic dilated cardiomyopathy (48, 49, 51).

Given the wide range of potentially fatal cardiac complications and the prevalence of cocaine use among young trauma patients, an unexplained cardiac arrest in an injured or septic hospitalized patient should prompt a drug screen. Street drugs are available to postoperative patients through friends and "business" colleagues. Two factors make the risk of in-hospital illicit drug usage especially dangerous. First, the friend selects the "best" preparation, which is undiluted. Second, the cardiopulmonary reserve of the postoperative patient is reduced. This promotes a cardiac catastrophe when the patient snorts or smokes his so-called normal dose. After resuscitative efforts have failed, a postmortem drug screen will identify the real culprit and deter subsequent malpractice litigation directed toward some lethal and cryptic treatment error (52–54).

Gastrointestinal Complications. The most common and serious gastrointestinal complication of cocaine use is acute ischemia secondary to intense arterial vasoconstriction through cocaine-induced catecholamine stimulation of alpha-adrenergic receptors in the gastric and mesenteric vessels (55). Gastrointestinal ischemia may result in gastroduodenal ulceration and perforation usually within 3 days of cocaine use (8, 55–57). In contrast to peptic ulcer disease, where ulceration and perforation present more commonly in the duodenal bulb in the 48- to 65-yr age group, cocaine-induced foregut ulceration and perforation present in younger patients and often occur in the prepyloric region, the pyloric canal, or the greater curvature of the stomach (8). Cocaine's anticholinergic actions produce gastric hypomotility, delayed gastric emptying, and prolonged exposure to gastric acid, thus contributing to ulcer formation. Cocaine also acts directly on the medullary centers that regulate gastric motility and vasomotor activity (58). Delayed gastric emptying results in increased risk of pulmonary aspiration, particularly in a patient who is sedate or unconscious secondary to intoxication of traumatic brain injury.

Cocaine-induced mesenteric arterial vasoconstriction results in decreased intestinal blood flow, petechial hemorrhages, bowel edema, mucosal ulceration, necrosis, and perforation (59, 60). The patient will have constant pain in the mid abdomen associated with moderate tenderness, low-grade fever, and leukocytosis (55). The high occurrence of cocaine use at the time of blunt abdominal trauma compounds the clinical assessment. The ischemic insult from cocaine is focal so that the full thickness necrosis may be pinpoint, small, and contained by adjacent viscera (Fig. 1). Thus, exploratory laparotomy for suspected bowel rupture leads to the diagnosis of focal full-thickness ischemia, which would likely have responded to bowel rest and antimicrobials (Fig. 2) (55).

Cocaine-induced acute and subacute ischemic colitis is less common but still challenging. The endoscopically visualized lesions are usually segmental and include pseudopolyps, ulcers, and focal mucosal hemorrhage, typically confined to the hindgut in contrast to the classic form of diffuse ischemic colitis (61). This observation rules out hemorrhagic shock as the precipitating insult. Expectant therapy is recommended. When celiotomy is performed for suspected peritonitis due to hollow viscus rupture, the colon perforation due to cocaine ingestion should be excised. Microscopic studies will confirm the focal nature of the ischemic necrosis and perforation (Fig. 3).

Cocaine-induced splenic infarction and hemorrhage has also been reported. The infarction results from intense vasospasm; hemorrhage ensues after the vasospasm resolves. Splenic hemorrhage may also occur from arteriolar rupture from cocaine-induced hypertension (62). Patients may present with vague and constant left upper quadrant pain, which is more severe than that associated with a traumatic splenic hematoma. The radiographic finding may mimic a traumatic hematoma. Frank hemorrhage may necessitate celiotomy expecting to find blunt splenic trauma. The finding of focal rupture of the splenic surface without large rents leads the surgeon to suspect a cocaine-induced rupture.

Cocaine-related gastrointestinal complications are sometimes seen in "body packers" or "mules," who smuggle cocaine intracorporeally. Body packers swallow multiple packets of cocaine along

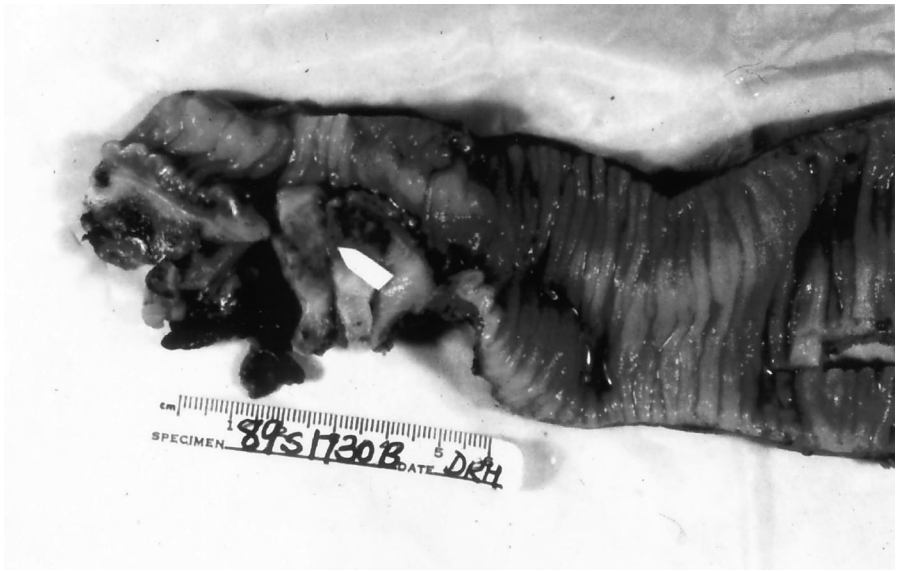

Figure 1. Resected small bowel showing pinpoint necrosis at a site of cocaine-induced focal perforation (*arrow*), which was walled off by adjacent bowel. Preoperation diagnosis was blunt rupture of bowel after assault.

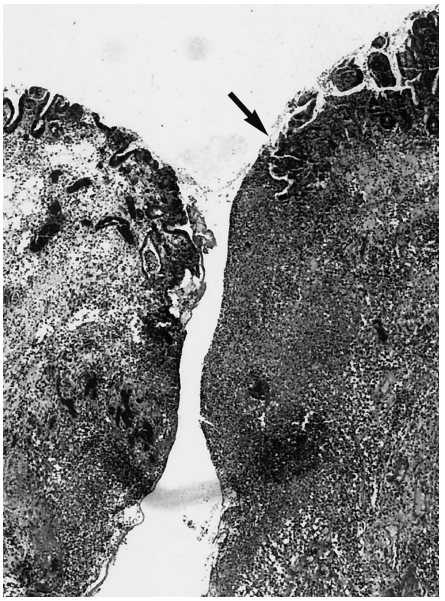

Figure 2. Photomicrograph shows focal mucosal necrosis (*arrow*) and underlying submucosal inflammation and fibrosis (hematoxylin and eosin, ×40).

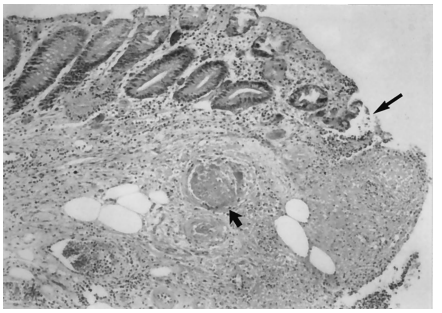

Figure 3. Photomicrograph of perforated sigmoid colon after a motor vehicle crash shows mucosal necrosis (*long arrow*) and submucosal inflammation with thrombosed submucosal blood vessel (*short arrow*). Preoperative diagnosis was blunt rupture of colon (hematoxylin and eosin, ×150)

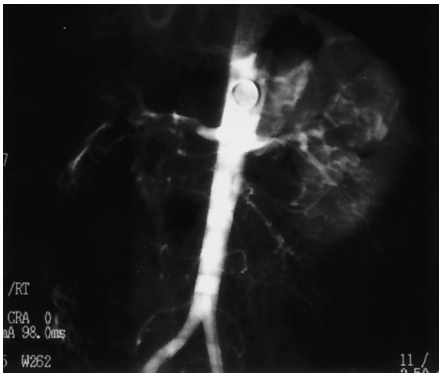

Figure 4. Aortogram of a patient who had a high-speed motor vehicle crash while on cocaine shows bilateral renal artery clots and aortic thrombosis. He developed renal tubular necrosis after emergent thrombectomies. From Webber J, Kline RA, Lucas CE: Aortic thrombosis associated with cocaine use: Report of two cases. *Ann Vasc Surg* 1999; 13:302–304.

with a constipating agent. Once through customs, they use laxatives or enemas to retrieve the packets in the stool. Each packet contains 3–7 g of cocaine, a fatal dose if a packet ruptures and the cocaine is absorbed. The ingested cocaine packets may also cause a mechanical bowel obstruction. Once ruptured, the surviving patient may experience all of the complications of cocaine toxicity, including giant gastric ulceration. Asymptomatic body packers can be managed with cathartics and observation. Surgical intervention is recommended if the packets fail to clear after 3–4 days of medical management (63).

Renal Complications. Cocaine induces direct and indirect renal complications. The direct complications include acute renal infarction resulting from renal arterial vasospasm and thrombosis caused by an imbalance between thromboxane and prostacyclin synthesis in the damaged renal artery endothelial cells (Fig. 4) (64, 65). Cocaine-induced renal artery arteriosclerosis is another mechanism for renal infarction and subsequent renal failure (66). Cocaine induces macrophage interleukin-6 production and subsequent mesangial cell proliferation, which results in focal segmental glomerulosclerosis (8).

Renal failure also occurs in about 30% of patients with cocaine-induced traumatic or nontraumatic rhabdomyolysis. Cocaine induces vasoconstriction of intramuscular arteries, which results in muscular ischemia, myofibrillar degeneration, and acute rhabdomyolysis (67, 68). Rhabdomyolysis can also result from cocaine-induced seizures with coma and compression of a major muscle group (68). The large amount of free myoglobin aggravates the renal vasoconstrictive insult and causes renal tubular obstruction and decreased glomerular filtration resulting in acute renal failure. Patients present with muscle pain and tenderness, hyperkalemia, hyperphosphatemia, and hyperuricemia. Serum creatinine is increased, and the extent of rhabdomyolysis is reflected by the high levels of plasma creatinine kinase, which may exceed 100,000 untis/L. Tissue thromboplastin may be released into the circulation and precipitate disseminated intravascular coagulation, which is usually fatal (67). These renal complications can be ameliorated by generous hydration to optimize renal blood flow.

Vascular Complications. Cocaine induces small and large vessel occlusion by both vasospasm and thrombosis with or without endothelial cell injury. The result may be focal necrosis or widespread ischemia and infarction depending on the diameter of the occluded vessel. Chronic cocaine use causes an increase in adventitial mast cells and atherosclerosis of the

vessels, which predisposes to end-organ ischemia in young patients (69).

Arterial thrombosis is secondary to the cocaine-induced decrease in protein C and antithrombin III levels, increase in plasminogen activator inhibitor activity, and increase in platelet activation and aggregation (18, 19, 20). Thrombosis of large vessels including the aorta has been reported and typically presents within 12 hrs of cocaine exposure (Fig. 4) (8). When a patient presents with long bone fractures obtained under the influence of cocaine, the clinical picture may be confusing. Cocaine-induced rhabdomyolysis of the leg muscles after intramedullary rodding of the ipsilateral femur may be mistaken for direct blunt injury of the leg. The cocaine-induced muscle injury is more likely to cause a more severe elevation of tissue pressure compared with direct external trauma. When a patient has both external injury and cocaine-induced injury, the decision regarding fasciotomy should be based on sequential measurements of tissue pressure. The clinical conundrum is even more complex when the effects of cocaine-induced large-vessel occlusion are added (Fig. 5). Thrombectomy followed by anticoagulation in this setting may be limb saving (70).

When named intraabdominal arteries become occluded, the mechanism of action is thought to be stasis in the vasovasorum leading to intimal injury and platelet aggregation. Treatment is determined by the end-organ effects. Mesenteric artery occlusion without necrosis, renal artery occlusion without renal shutdown, and aortic thrombosis without distal ischemia (Fig. 4) can be treated by anticoagulation and careful monitoring in a critical care setting. When end-organ failure or tissue necrosis is threatened, emergency thrombectomy is needed (70).

Figure 5. Arteriogram showing occlusion of the right profunda femoris artery in a patient with a right femur fracture after a motor vehicle crash. Subsequent rhabdomyolysis led to acute renal failure.

Aortic dissection secondary to cocaine may also occur. The dissection begins with an intimal tear secondary to a combination of repeated lateral motion of the aorta near the beating heart and the hemodynamic shear forces of the bloodstream enhanced by cocaine-induced hypertension. A subintimal hematoma forms and propagates as a result of sustained hypertension; this may be a chronic process. If untreated, the dissection is likely to rupture (71, 72). The clinical syndrome of excruciating sudden chest pain that is "tearing" or "ripping" may be confused with blunt aortic disruption after severe thoracic injury. The goal of treatment is control of the hypertension, which becomes easier as the cocaine level decreases. Hypotension is an ominous sign and suggests acute aortic regurgitation with proximal dissection and cardiac failure, pericardial tamponade, or myocardial infarction (72).

Maternal-Fetal and Neonatal Complications. Das and Laddu (73) reported that 11% of pregnant women are substance abusers, with cocaine being the favorite drug. Cocaine causes direct and indirect insult to the growing fetus. Cocaine crosses the placenta by simple diffusion and accumulates in the fetal plasma in higher than expected concentrations secondary to rapid diffusion, decreased maternal and fetal cholinesterases, which metabolize cocaine, and increased norcocaine synthesis by the pregnant patient (14, 74). At the maternal level, cocaine is known to cause spontaneous abortions, abruptio placenta, placenta previa, and stillbirths (75, 76). Cocaine induces spontaneous abortion by increasing maternal plasma norepinephrine levels, which cause uterine contractions through alpha- and beta-adrenergic receptor stimulation, constriction of placental vessels, and decrease of fetal blood flow (76). Fetal hypoxia leads to intrauterine growth retardation and developmental abnormalities of the brain, heart, great vessels, and gastrointestinal and urogenital tracts. Fetal hypoxia also impairs fetal central nervous system autoregulation, which increases cerebral blood flow and precipitates hemorrhage. Thirty-five percent of documented cocaine-exposed fetuses have ultrasonographic evidence of central nervous system cavities, ventricular enlargement, infarction, subarachnoid hemorrhage, intraventricular hemorrhage, or subependymal hemorrhage (77). Cocaine also causes direct intense stimulation of the central nervous system by catecholamines or infarction, through cocaine-induced fetal hypertension, which precipitates seizures in the neonatal period (78). Thirty percent of neonates exposed to cocaine in utero experience withdrawal manifested by seizure, lethargy, feeding problems, hyperactive reflexes, vomiting, and diarrhea. Cocaine also induces ventricular tachycardia and coronary artery spasm with myocardial ischemia in the neonate (8). On follow-up, cocaine-exposed neonates demonstrate neurobehavioral deficits and long-term cognitive and developmental delays (79). These myriad of maternal and fetal events create havoc when a woman presents with an acute surgical emergency in the third trimester of pregnancy under the influence of cocaine. Routine drug screens will alert the trauma surgeon and the obstetrician of the potential for fetal distress or sudden expulsion of a potentially viable fetus.

Psychiatric Complications. A comorbid psychiatric disorder is present in 60% to 70% of cocaine users. These abnormalities include mood disorders, bipolar manifestation, attention deficit, panic attacks, paranoid ideation, and a behavior pattern that may be conducive to violence and homicidal intent (11). Forty percent of cocaine and opiate users are likely to be injured and, when injured, are more likely to suffer from posttraumatic stress. Incarceration and expulsion from school are common features of cocaine users. Cocaine-associated delirium is now better recognized. Agitated delirium accounts for 10% of cocaine deaths. This is seen in patients with modest cocaine blood levels but high levels of benzylecgonine, the principal cocaine metabolite. Treatment, when patients survive long enough to reach the hospital, is supportive (80–83). Recognition of cocaine-induced mental aberrations is problematic in patients with traumatic brain injury or stroke. The coexistence of alcohol exposure further impairs accurate diagnosis. Psychiatric evaluation may be necessary for the management of acute mental aberrations and long-term follow-up in drug treatment centers.

Recognition of the signs and symptoms of cocaine toxicity help anticipate the subsequent organ dysfunction and implement earlier organ system support.

CONCLUSION

Cocaine exposure in trauma patients and critically ill patients complicates resuscitation and treatment. A myriad of multiple organ toxicities, in the authors' experience, aggravate the detrimental effects of hemorrhagic shock and sepsis, leading to higher mortality rate. Recognition of these multiple organ sequelae of cocaine is essential for the treating physician to provide optimal care and avoid otherwise unforeseen complications. Identification of cocaine use can only be provided by an aggressive approach by the physician team. This approach should include routine questioning of patients about substance utilization and routine toxicology screen at the time of admission to identify which patients may be at risk for these sequelae. A repeat toxicology screen may be utilized in patients who have unusual detrimental effects to treatment at a time when recovery should be clear. Sudden death in the patient who is improving and is almost ready for discharge should be suspected of being related to the ingestion of cocaine typically brought in by patient friends. The early identification of cocaine intoxication should lead the physician to increase the level of monitoring for detrimental organ sequelae, which may be implemented in an intensive care environment. Earlier identification of organ changes then helps facilitate therapy. Consequently, the pragmatic role of early toxicological screening clearly affects treatment decision and will likely lead to improved patient outcome.

Once cocaine intoxication is identified, it may be difficult to determine which are the detrimental effects of the cocaine as opposed to the organ effects of hemorrhagic shock and/or sepsis because many of the multiple organ effects of cocaine parallel those effects, which are seen in the systemic inflammatory response. Early identification of cocaine intoxication will also identify patients in whom treatment with beta blockade, sedatives, or anticonvulsants might be beneficial.

Although reliable data on the effects of cocaine on healthcare cost is not available, the authors believe that the organ function changes, which are made worse by the presence of cocaine, lead to increased need for critical care beds and a prolonged length of stay.

REFERENCES

1. Gay GR, Inaba DS, Sheppard CW, et al: Cocaine: History, epidemiology, human pharmacology, and treatment. *Clin Toxicol* 1975; 8:149–178
2. Christenson EM: Coca, divine plant of the Incas. *Anaesthesia* 1946; 2:4–12
3. Cohen S: Cocaine. *JAMA* 1975; 231:74–75
4. Musto DF: A study in cocaine. *JAMA* 1968; 204:125–130
5. Schoenberg BS: Coke's the one: The centennial of the "ideal brain tonic" that became a symbol of America. *South Med J* 1988; 81: 69–74
6. Bailey BJ: Looking back at a century of cocaine use and abuse. *Laryngoscope* 1996; 106:681–683
7. Jonnes J: The rise of the modern addict. *Am J Public Health* 1995; 85:1157–1162
8. Boghdadi MS, Henning RJ: Cocaine: Pathophysiology and clinical toxicology. *Heart Lung* 1997; 26:466–481
9. Marzuk PM, Tardiff K, Leon AC, et al: Fatal injuries after cocaine use as a leading cause of death among young adults in New York city. *N Engl J Med* 1995; 332:1753–1757
10. Levy RS, Hebert CK, Munn BG, et al: Drug and alcohol use in orthopedic trauma patients: A prospective study. *J Orthop Trauma* 1996; 10:21–27
11. Lucas CE, Ledgerwood AM, Kline RA. Alcohol and drugs. *In:* Trauma. Mattox KL, Feliciano DV, Moore EE (Eds). New York: NY, McGraw-Hill, 2000, pp 1059–1074
12. Soderstrom CA, Tandon M, Dischinger PC, et al. Epidemic increases in cocaine and opiate use by trauma center patients: Documentation with a large clinical toxicology database. *J Trauma* 2001;51:557–564.
13. Tran M: Drugs war is 'futile exercise.' *Guardian Weekly* June 21, 1998, pp 5
14. Hollister LE: Drugs of abuse. *In:* Basic and Clinical Pharmacology. Katzung BG (Ed). Norwalk, CT, Appleton & Lange, 1992, pp 437–449
15. Leshner AI: Molecular mechanisms of cocaine addiction. *N Engl J Med* 1996; 335: 128–129
16. Baldwin GC, Tashkin DP, Buckley DM, et al: Marijuana and cocaine impair alveolar macrophage function and cytokine production. *Am J Respir Crit Care Med* 1997; 156: 1606–1613
17. Baldwin GC, Buckley DM, Roth MD, et al: Acute activation of circulating polymorphonuclear neutrophils following *in vivo* administration of cocaine. *Chest* 1997; 111: 698–705
18. Heesch CM, Negus BH, Steiner M, et al: Effects of *in vivo* cocaine administration on human platelet aggregation. *Am J Cardiol* 1996; 78:237–239
19. Chokshi SK, Miller G, Rongione A, et al: Cocaine and cardiovascular diseases: The leading age. *Cardiology* 1989; III:1–6
20. Moliterno DJ, Lange RA, Gerard RD, et al: Influence of intranasal cocaine on plasma constituents associated with endogenous thrombosis and thrombolysis. *Am J Med* 1994; 96:492–496
21. Fahim I, Ismail M, Osman OH: Hypothermic effect of cocaine in rats. *West Afr J Pharmacol Drug Res* 1975; 2:48–56
22. Wicchman BE, Spratto GR: Body temperature response to cocaine and diazepam in morphine-treated rats. *Pharmacology* 1982; 25:308–319
23. Long SF, Davis WM, Waters IW: Additive hypothermic effects of cocaine and nicardipine in guinea-pigs. *Gen Pharmacol* 1994; 25:1585–1590
24. Maurer HH: Liquid chromatography-mass spectrometry in forensic and clinical toxicology. *J Chromatogr B Biomed Sci Appl* 1998; 713:3–25
25. Kintz P, Samyn N: Use of alternative specimens: Drugs of abuse in saliva and doping agents in hair. *Ther Drug Monit* 2002; 24: 239–246
26. Dickson PH, Lind A, Studts P, et al: The routine analysis of breast milk for drugs of abuse in a clinical toxicology laboratory. *J Forensic Sci* 1994; 39:207–214
27. Moeller MR, Steinmeyer S, Kraemer T: Determination of drugs of abuse in blood. *J Chromatogr B Biomed Sci Appl* 1998; 713: 91–109
28. Linder MW, Bosse GM, Henderson MT, et al: Detection of cocaine metabolite in serum and urine: Frequency and correlation with medical diagnosis. *Clin Chim Acta* 2000; 295: 179–185
29. Maurer HH: Systematic toxicological analysis of drugs and their metabolites by gas chromatography-mass spectrometry. *J Chromatogr* 1992; 580:3–41
30. Qureshi AI, Akbar MS, Czander E, et al: Crack cocaine use and stroke in young patients. *Neurology* 1997; 48:341–345
31. Kaufman MJ, Levin JM, Ross MH, et al: Cocaine-induced cerebral vasoconstriction detected in humans with magnetic resonance angiography. *JAMA* 1998; 279:376–380
32. Gradon JD, Wityk R: Diagnosis of probable cocaine-induced cerebral vasculitis by magnetic resonance angiography. *South Med J* 1995; 88:1264–1266
33. Merkel PA, Koroshetz WJ, Irizarry MC, et al:

Cocaine-associated cerebral vasculitis. *Semin Arthritis Rheum* 1995; 25:172–183
34. Aggrawal SK, Williams V, Levine SR, et al: Cocaine-associated intracranial hemorrhage: Absence of vasculitis in 14 cases. *Neurology* 1996; 46:1741–1743
35. Nolte KB, Brass LM, Fletterick CF: Intracranial hemorrhage associated with cocaine abuse: A prospective autopsy study. *Neurology* 1996; 46:1291–1296
36. Dhuna A, Pascual-Leone A, Langendorf F, et al: Epileptogenic properties of cocaine in humans. *Neurotoxicology*. 1991; 12:621–626.
37. Cruz R, Davis M, O'Neil H, et al: Pulmonary manifestations of inhaled street drugs. *Heart Lung* 1998; 27:297–305
38. Albertson TE, Walby WF, Derlet RW: Stimulant-induced pulmonary toxicity. *Chest* 1995; 108:1140–1149
39. Sousa O, Rowley S: Otorhinolaryngologic symptoms caused by the intranasal abuse of cocaine: Report of a case. *Rev Med Panama* 1994; 19:55–60
40. Perper JA, Van Thiel DH: Respiratory complications of cocaine abuse. *Recent Dev Alcohol* 1992; 10:363–377
41. Underdahl JP, Chiou AG: Preseptal cellulitis and orbital wall destruction secondary to nasal cocaine abuse. *Am J Ophthalmol* 1998; 125:266–268
42. Haim DY, Lippmann ML, Goldberg SK, et al: The pulmonary complications of crack cocaine. *Chest* 1996; 107:233–240
43. Averbach M, Casey KK, Frank E: Near-fatal status asthmaticus induced by nasal insufflation of cocaine. *South Med J* 1996; 89: 340–341
44. Tashkin DP, Kleerup EC, Koyal SN, et al: Acute effects of inhaled and IV cocaine on airway dynamics. *Chest* 1996; 110:904–910
45. Kleerup EC, Wong M, Marques-Magallanes JA, et al: Acute effects of intravenous cocaine on pulmonary artery pressure and cardiac index in habitual crack smokers. *Chest* 1997; 111:30–35
46. Yakel DL, Eisenberg MJ: Pulmonary artery hypertension in chronic intravenous cocaine users. *Am Heart J* 1995; 130:398–399
47. Sullivan TR, Pierson DJ: Pneumomediastinum after freebase cocaine use. *AJR Am J Roentgenol* 1997; 168:84
48. Mouhaffel AH, Madu EC, Satmary WA, et al: Cardiovascular complications of cocaine. *Chest* 1995; 107:1426–1434
49. Thadani PV: NIDA conference report on cardiopulmonary complications of "crack" cocaine use. *Chest* 1996; 110:1072–1076
50. Pitts WR, Lange RA, Cigarroa JE, et al: Cocaine-induced myocardial ischemia and infarction: Pathophysiology, recognition, and management. *Prog Cardiovasc Dis* 1997; 40: 65–76
51. Pitts WR, Vongpatanasin W, Cigarroa JE, et al: Effects of the intracoronary infusion of cocaine on left ventricular systolic and diastolic function in humans. *Circulation* 1998; 97:1270–1273
52. Shen WK, Edwards WD, Hammill SC, et al: Sudden unexpected nontraumatic death in 54 young adults: A 30-year population-based study. *Am J Cardiol* 1995; 76:148–152
53. Krome RL, Ledgerwood A, Lucas CE: The hazards of drug addiction on a trauma ward. *Mich Med* 1971; 70:603–605
54. Weicht GT, Bernards CM: Remote cocaine use as a likely cause of cardiogenic shock after penetrating trauma. *Anesthesiology* 1996; 85:933–935
55. Herrine SK, Park PK, Wechsler RJ: Acute mesenteric ischemia following intranasal cocaine use. *Dig Dis Sci* 1998; 43:586–589
56. Sharma R, Organ CH, Hirvela ER, et al: Clinical observation of the temporal association between crack cocaine and duodenal ulcer perforation. *Am J Surg* 1997; 174:629–633
57. Lin C, Gabram SG, Roskam SA, et al: Perforated peptic ulcer and cocaine use. *Contemp Surg* 1999; 54:109–112
58. Abramson DL, Gertler JP, Lewis T, et al: Crack-related perforated gastropyloric ulcer. *J Clin Gastroenterol* 1991; 13:17–19
59. Mizrahi S, Laor D, Stamler B: Intestinal ischemia induced by cocaine abuse. *Arch Surg* 1988; 123:394
60. Nalbandian H, Sheth N, Dietrich R, et al: Intestinal ischemia caused by cocaine ingestion: Report of two cases. *Surgery* 1985; 97: 374–376
61. Niazi M, Kondru A, Levy J, et al: Spectrum of ischemic colitis in cocaine users. *Dig Dis Sci* 1997; 42:1537–1541
62. Homler HJ: Nontraumatic splenic hematoma related to cocaine abuse. *West J Med* 1995; 163:160–161
63. Miller JS, Hendren SK, Liscum KR: Giant gastric ulcer in a body packer. *J Trauma* 1998; 45:617–619
64. Kramer RK, Turner RC: Renal infarction associated with cocaine use and latent protein C deficiency. *South Med J* 1993; 86: 1436–1438
65. Heng MC, Haberfeld G: Thrombotic phenomena associated with intravenous cocaine. *J Am Acad Dermatol* 1987; 16:462–468
66. Fogo A, Superdock R, Atkinson JB: Severe arteriosclerosis in the kidney of a cocaine addict. *Am J Kidney Dis* 1992; 20:513–515
67. Roth D, Alarcon FJ, Fernandez J, et al: Acute rhabdomyolysis associated with cocaine intoxication. *N Engl J Med* 1988; 319:673–677
68. Singhal PC, Rubin B, Peters A, et al: Rhabdomyolysis and acute renal failure associated with cocaine abuse. *Clin Toxicol* 1990; 28: 321–330
69. Kolodgie FD, Virmani R, Cornhill F, et al: 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; 17:1553–1560
70. Webber J, Kline RA, Lucas CE: Aortic thrombosis associated with cocaine use: Report of two cases. *Ann Vasc Surg* 1999; 13:302–304
71. Rashid J, Eisenberg MJ, Topol EJ: Cocaine-induced aortic dissection. *Am Heart J* 1996; 132:1301–1304
72. Chang RA, Rossi NF: Intermittent cocaine use associated with recurrent dissection of the thoracic and abdominal aorta. *Chest* 1995; 106:1758–1762
73. Das G, Laddu A: Cocaine: Friend or foe? Part I. *Int J Clin Pharmacol Ther* 1993; 31: 449–455
74. Chasnoff IJ, Lewis DE, Griffith DR, et al: Cocaine and pregnancy: Clinical and toxicological implications for the neonate. *Clin Chem* 1989; 35:1276–1278
75. Macones GA, Sehdev HM, Parry S, et al: The association between maternal cocaine use and placenta previa. *Am J Obstet Gynecol* 1997; 177:1097–1100
76. Hurd WW, Betz AL, Dombrowski MP, et al: Cocaine augments contractility of the pregnant human uterus by both adrenergic and nonadrenergic mechanisms. *Am J Obstet Gynecol* 1998; 178:1077–1081
77. Dixon SD, Bejar R: Echoencephalographic findings in neonates associated with maternal cocaine and methamphetamine use: Incidence and clinical correlated. *J Pediatr* 1989; 115:770–778
78. Singer LT, Yamashita TS, Hawkins S, et al: Increased incidence of intraventricular hemorrhage and developmental delay in cocaine-exposed, very low birth weight infants. *J Pediatr* 1994; 24:765–771
79. Singer LT, Arendt R, Minnes S, et al: Cognitive and motor outcomes of cocaine-exposed infants. *JAMA* 2002; 287:1952–1960
80. Morrow CE, Bandstra ES, Anthony JC, et al: Influence of prenatal cocaine exposure on full-term infant neurobehavioral functioning. *Neurotoxicol Teratol* 2001; 23:533–544
81. Wetli CV, Mash D, Karch SB: Cocaine-associated agitated delirium and the neuroleptic malignant syndrome. *Am J Emerg Med* 1996; 14:425–428
82. Mirchandani HG, Rorke LB, Sekula-Perlman A, et al: Cocaine-induced agitated delirium, forceful struggle, and minor head injury. *Am J Forensic Med Pathol* 1994; 15:95–99
83. Ruttenber AJ, Lawler-Heavner J, Yin M, et al: Fatal excited delirium following cocaine use: Epidemiologic findings provide new evidence for mechanisms of cocaine toxicity. *J Forensic Sci* 1997; 42:25–31