

*Medical Progress***CARDIOVASCULAR COMPLICATIONS  
OF COCAINE USE**

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**T**HE deaths of several celebrities in recent years in association with the nontherapeutic use of cocaine have focused widespread attention on the problem of cocaine abuse. In 1999, an estimated 25 million Americans admitted that they had used cocaine at least once; 3.7 million had used it within the previous year; and 1.5 million were current users. During the same year, cocaine was mentioned in 30 percent of all drug-related visits to emergency departments.<sup>1</sup> Cocaine is the most commonly used illicit drug among subjects seeking care in hospital emergency departments or drug-treatment centers. In addition, it is the most frequent cause of drug-related deaths reported by medical examiners.<sup>1</sup>

Cocaine use rose to epidemic levels in the early and mid-1980s, after which it declined in prevalence. However, between 1994 and 1998, the number of new cocaine users per year increased 82 percent, from 514,000 to 934,000. Several factors account for this recent increase in cocaine use, including the ease of its administration, the increased availability and purity of the drug, reduced cost, and the misperception that the recreational use of cocaine is safe. In a recent survey conducted by the Department of Health and Human Services, only 50 percent of young people expressed the belief that monthly cocaine ingestion carries a great risk of harm.<sup>2</sup> In fact, as cocaine abuse has become widespread, the number of cocaine-related cardiovascular events, including angina pectoris, myocardial infarction, cardiomyopathy, and sudden death from cardiac causes, has increased dramatically.

**PHARMACOLOGY AND MECHANISMS  
OF ACTION**

Cocaine (benzoylecgonine) is an alkaloid extracted from the leaf of the *Erythroxylon coca* bush, which grows primarily in South America. It is available in two forms: the hydrochloride salt and the "free base." Cocaine hydrochloride is prepared by dissolving the alkaloid in hydrochloric acid to form a water-soluble powder or granule that decomposes when heated. It can be taken orally, intravenously, or intranasally,

the slang terms for which are "chewing," "mainlining," and "snorting," respectively. The free-base form is manufactured by processing the cocaine with ammonia or sodium bicarbonate (baking soda) to remove the hydrochloride. This form is heat-stable and melts at 98°C, which allows it to be smoked. It is known as "crack" because of the popping sound it makes when heated.

Since cocaine hydrochloride is well absorbed through all mucous membranes, abusers may achieve a high blood concentration by means of intranasal, sublingual, intravaginal, or rectal administration (Table 1). As compared with the intravenous injection of cocaine, the mucosal administration of the drug results in a slower onset of action, a later peak effect, and a longer duration of action. Euphoria occurs within seconds after crack cocaine is smoked and is short-lived. Crack cocaine is considered to be the most potent and addictive form of the drug.

Cocaine is metabolized by plasma and liver cholinesterases to water-soluble metabolites (primarily benzoylecgonine and ecgonine methyl ester), which are excreted in the urine.<sup>3</sup> The serum half-life of cocaine is 45 to 90 minutes; only 1 percent of the parent drug can be recovered in the urine after it is ingested. Thus, cocaine can be detected in blood or urine for only several hours after its use. However, its metabolites are detectable in blood or urine for 24 to 36 hours after ingestion, thereby providing a useful indicator of recent drug ingestion. Hair analysis provides an extremely sensitive marker of cocaine use in the preceding weeks or months, depending on the length of the hair analyzed.<sup>4</sup> Interestingly, the results of studies that have used hair analysis suggest that the prevalence of cocaine use may be three to five times as high as that estimated by standard surveys and interviews with patients.<sup>5,6</sup>

When applied locally, cocaine acts as an anesthetic because of its ability to inhibit membrane permeability to sodium during depolarization, thereby blocking the initiation and transmission of electrical signals. When given systemically, its effects are mediated through alterations in synaptic transmission. Cocaine blocks the presynaptic reuptake of norepinephrine and dopamine, producing an excess of these neurotransmitters at the site of the postsynaptic receptor (Fig. 1). In short, cocaine acts as a powerful sympathomimetic agent.

**COCAINE-RELATED MYOCARDIAL  
ISCHEMIA AND INFARCTION**

In 1982, Coleman et al.<sup>7</sup> reported an association between cocaine use and myocardial ischemia and infarction. Subsequently, many reports have documented cocaine-related myocardial ischemic events.<sup>8-10</sup> The risk of acute myocardial infarction is increased by a factor of 24 during the 60 minutes after the use of cocaine in persons who are otherwise at relatively low risk.<sup>11</sup> The occurrence of myocardial infarction after

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**TABLE 1. PHARMACOKINETICS OF COCAINE ACCORDING TO THE ROUTE OF ADMINISTRATION.**

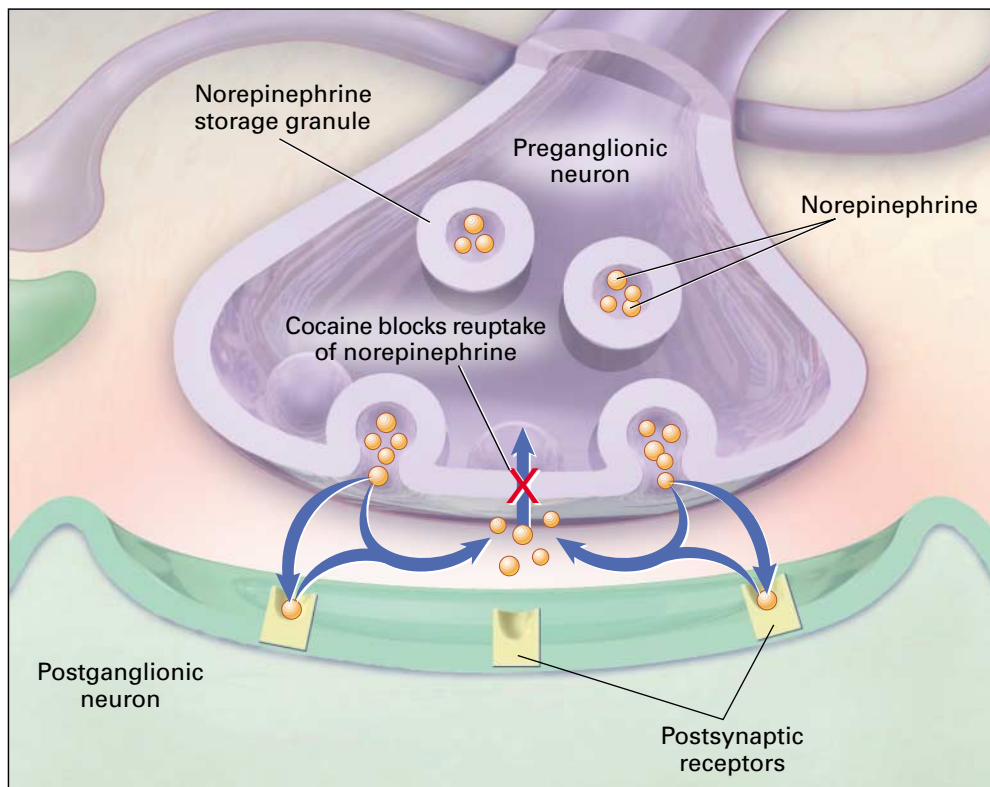
ROUTE OF ADMINISTRATION	ONSET OF ACTION	PEAK EFFECT	DURATION OF ACTION
Inhalation (smoking)	3–5 sec	1–3 min	5–15 min
Intravenous	10–60 sec	3–5 min	20–60 min
Intranasal or other mucosal	1–5 min	15–20 min	60–90 min

cocaine use is unrelated to the amount ingested, the route of administration, and the frequency of use; it has been reported with doses ranging from 200 to 2000 mg, after ingestion by all routes, and in habitual as well as first-time users.

Persons presenting to the emergency department with nontraumatic chest pain should be questioned about cocaine use, since such pain is the most common symptom in cocaine users.<sup>12</sup> Of patients who come to the emergency department with nontraumatic chest pain, 14 to 25 percent in urban hospitals and

7 percent in suburban hospitals have detectable levels of cocaine or cocaine metabolites in their urine.<sup>13</sup>

Approximately 6 percent of patients who come to the emergency department with cocaine-associated chest pain have enzymatic evidence of myocardial infarction.<sup>14</sup> Patients with cocaine-related myocardial infarction cannot be distinguished from those without this condition on the basis of such clinical variables as the time of onset of pain, the location of the pain, its quality or duration, the presence or absence of a history of chest pain or myocardial infarction, and the presence or absence of traditional risk factors for atherosclerosis.<sup>14</sup> Most patients with cocaine-related myocardial infarction are young, nonwhite, male cigarette smokers without other risk factors for atherosclerosis who have a history of repeated use of cocaine.<sup>11,14-16</sup> About half the patients with cocaine-related myocardial infarction have no evidence of atherosclerotic coronary artery disease on subsequent angiography.<sup>8,17</sup> Therefore, when patients with no or few risk factors for atherosclerosis, especially those who are young or have a history of substance abuse, present with acute myocardial infarction, urine and blood samples should be analyzed for cocaine and its metabolites.



**Figure 1. The Mechanism by Which Cocaine Alters Sympathetic Tone.**

Cocaine blocks the reuptake of norepinephrine by the preganglionic neuron (red X), resulting in excess amounts of this neurotransmitter at receptor sites on the postganglionic neuron.

The accurate identification of patients with cocaine-related myocardial infarction may be difficult for at least two reasons. First, the electrocardiogram may be abnormal in many patients with chest pain after cocaine use, even in the absence of myocardial infarction. The electrocardiogram is reportedly abnormal in 56 to 84 percent of patients with cocaine-related chest pain, and as many as 43 percent of cocaine abusers without myocardial infarction meet the electrocardiographic criterion for the initiation of reperfusion therapy (ST-segment elevation of at least 0.1 mV in two or more contiguous leads).<sup>14,18</sup> The sensitivity of the electrocardiogram for detecting myocardial infarction is reported to be 36 percent, its specificity 90 percent, its positive predictive value 18 percent, and its negative predictive value 96 percent.<sup>14</sup> The high failure rate of the electrocardiogram in identifying patients with cocaine-related myocardial infarction results, at least in part, from a high incidence of early repolarization abnormalities in young persons in the general population.

The second reason why it is difficult to identify cocaine-related myocardial infarction is that serum creatine kinase concentrations are not a reliable indicator of myocardial injury, since they are elevated in about half of cocaine users who do not have myocardial infarction. This elevation of serum creatine kinase is presumably due to rhabdomyolysis.<sup>18,19</sup> Accordingly, serum troponin concentrations, which are more sensitive and specific for the detection of myocardial infarction, should be measured in patients in whom cocaine-related myocardial infarction is suspected.

Cardiovascular complications resulting from cocaine-related myocardial infarction are relatively uncommon, with ventricular arrhythmias occurring in 4 to 17 percent of patients hospitalized with cocaine-related myocardial infarction, congestive heart failure in 5 to 7 percent, and death in less than 2 percent.<sup>15</sup> This low incidence of complications is due, at least in part, to the young age of most patients with this condition. Most complications occur within 12 hours after the initial presentation at the hospital. In those who have been discharged from the hospital, continued cocaine use and recurrent chest pain are common, and occasionally a patient has recurrent nonfatal myocardial infarction or dies.<sup>16</sup>

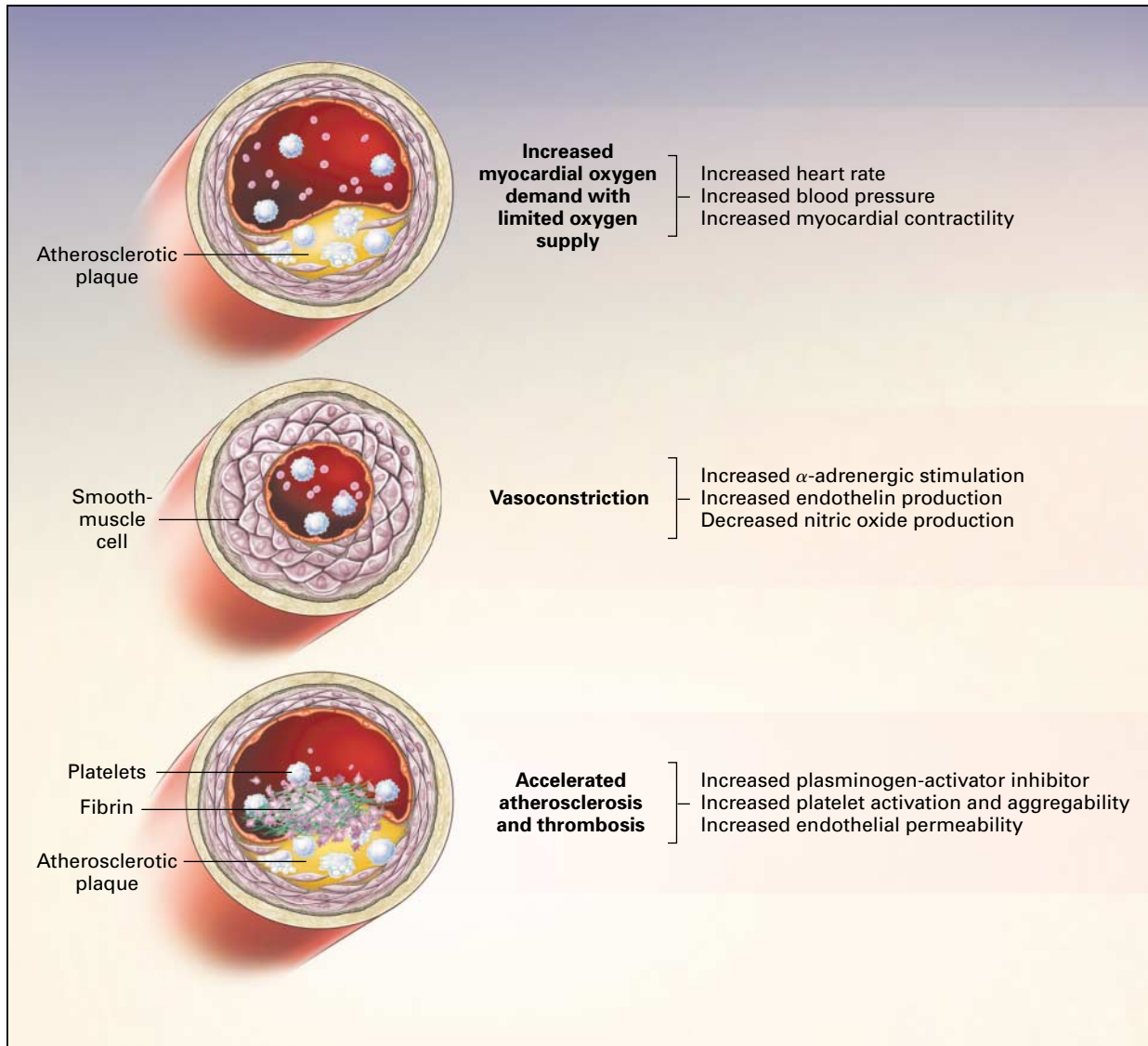
The pathogenesis of cocaine-related myocardial ischemia and infarction is probably multifactorial and includes one or more of the following elements: an increased myocardial oxygen demand in the face of a limited or fixed supply, marked vasoconstriction of the coronary arteries, and enhanced platelet aggregation and thrombus formation (Fig. 2). Cocaine induces an increase in the three major determinants of the myocardial oxygen demand: the heart rate, the systemic arterial pressure, and left ventricular contractility. At the same time, the ingestion of even small amounts of the drug causes vasoconstriction of the epicardial coronary

arteries<sup>20</sup> — so-called inappropriate vasoconstriction, in that the myocardial oxygen supply decreases even as the demand increases. Although cocaine induces vasoconstriction in both normal and diseased segments of the coronary arteries, its effects are more pronounced in the diseased segments.<sup>21</sup> As a result, cocaine users with atherosclerotic coronary artery disease are probably at greater risk for an ischemic event after cocaine use than are cocaine users without coronary artery disease. Cocaine-induced vasoconstriction of the coronary arteries is primarily a result of the stimulation of coronary arterial  $\alpha$ -adrenergic receptors, since it may be reversed with phentolamine (an  $\alpha$ -adrenergic antagonist)<sup>20</sup> and is exacerbated by propranolol (a  $\beta$ -adrenergic antagonist).<sup>22</sup> Cocaine also causes increased endothelial production of endothelin (a potent vasoconstrictor)<sup>23</sup> and decreased production of nitric oxide (a potent vasodilator)<sup>24</sup> — effects that may promote vasoconstriction.

Most patients with cocaine-related myocardial ischemia or infarction have chest pain within an hour after they have used cocaine, at a time when the blood cocaine concentration is highest.<sup>11,14</sup> However, others note the onset of symptoms several hours after the administration of the drug, when the blood concentration of cocaine is low or even undetectable.<sup>11,25,26</sup> With cocaine ingestion, the diameter of the coronary arteries decreases as the drug concentration rises, then returns to its base-line measurement as the drug concentration declines. Thereafter, as the concentrations of cocaine's major metabolites (benzoylecgonine and ecgonine methyl ester) rise, "delayed" (i.e., recurrent) vasoconstriction of the coronary arteries occurs.<sup>27</sup> Thus, the delayed or recurrent vasoconstriction of the coronary arteries appears to be caused by cocaine's major metabolites, which explains why myocardial ischemia or infarction may occur several hours after the ingestion of cocaine.

In addition to vasoconstriction, cocaine may induce thrombus formation in the coronary arteries.<sup>28</sup> Its use is associated with enhanced platelet activation and aggregability<sup>29-31</sup> as well as increases in the concentration of plasminogen-activator inhibitor,<sup>32</sup> which may promote thrombus formation. Premature atherosclerotic coronary artery disease has been observed in postmortem studies of long-term cocaine abusers and may provide the nidus for such thrombus formation.<sup>33</sup> In vitro studies have shown that cocaine causes structural defects in the endothelial-cell barrier, increasing its permeability to low-density lipoprotein<sup>34</sup> and enhancing the expression of endothelial adhesion molecules and leukocyte migration,<sup>35</sup> all of which are associated with the progression of atherosclerosis.

As noted above, cocaine-induced vasoconstriction of the coronary arteries can be reversed by phentolamine, an  $\alpha$ -adrenergic antagonist.<sup>20,36</sup> Conversely, propranolol — a  $\beta$ -adrenergic-blocking agent — exacerbates cocaine-induced vasoconstriction of the coronary



**Figure 2.** Mechanisms by Which Cocaine May Induce Myocardial Ischemia or Infarction.

Cocaine may cause increases in the determinants of myocardial oxygen demand when there is a limited oxygen supply (top), cause intense vasoconstriction of the coronary arteries (middle), or induce accelerated atherosclerosis and thrombosis (bottom).

arteries, and therefore it should not be used in patients with cocaine-related chest pain.<sup>22</sup> Since nitroglycerin<sup>37</sup> and verapamil<sup>38</sup> reverse cocaine-induced hypertension and vasoconstriction of the coronary arteries, they are the agents of choice for patients with cocaine-associated chest pain (Table 2). Labetalol, which has both  $\alpha$ - and  $\beta$ -adrenergic-blocking activity, reverses the cocaine-induced increase in systemic arterial pressure but exerts no demonstrable effect on cocaine-induced vasoconstriction of the coronary arteries.<sup>39,40</sup> Aspirin should be administered to patients with cocaine-induced myocardial ischemia to inhibit platelet aggregation. Benzodiazepines may also be helpful, since

they reduce the heart rate and the systemic arterial pressure<sup>41</sup>; in animals, they also attenuate cocaine's toxic effects on the heart and the nervous system. Because of the limited experience with thrombolytic therapy in patients with cocaine-related infarction,<sup>42</sup> reports of catastrophic complications associated with its use in cocaine users,<sup>43</sup> and the difficulty involved in using standard electrocardiographic criteria to identify myocardial infarction,<sup>18</sup> we caution against the routine use of thrombolytic therapy in patients who may have cocaine-related infarction. Thrombolytic therapy should be considered only after treatment with oxygen, aspirin, nitrates, and benzodiazepines has failed,

**TABLE 2.** RECOMMENDATIONS OF THE AMERICAN HEART ASSOCIATION FOR THE TREATMENT OF COCAINE-RELATED MYOCARDIAL ISCHEMIA OR INFARCTION.

<b>First-line agents</b>
Oxygen
Aspirin
Nitroglycerin
Benzodiazepines
<b>Second-line agents</b>
Verapamil
Phentolamine
Thrombolytic agent or primary angioplasty (after demonstration by arteriography of an occluded coronary artery)
<b>Agent to be avoided</b>
Propranolol

and when immediate coronary angiography and angioplasty are not available (Table 2).

The recently revised guidelines of the American Heart Association for emergency cardiovascular care<sup>44,45</sup> recommend nitroglycerin and benzodiazepines as first-line agents for patients with cocaine-related myocardial ischemia or infarction and phentolamine as a second-line agent; propranolol is contraindicated (Table 2). Thrombolysis is not recommended unless evidence of evolving myocardial infarction persists despite medical therapy and an occluded coronary artery is shown to be present on angiography. Thrombolysis is contraindicated if uncontrolled, severe systemic arterial hypertension is present.

#### COCAINE, CIGARETTE SMOKING, AND ALCOHOL USE

Many patients with cocaine-associated angina pectoris or myocardial infarction are cigarette smokers who admit to smoking while using cocaine. Cigarette smoking induces vasoconstriction of the coronary arteries through an  $\alpha$ -adrenergic mechanism similar to that of cocaine.<sup>46</sup> In fact, recent studies have demonstrated that the deleterious effects of cocaine on myocardial oxygen supply and demand are exacerbated substantially by concomitant cigarette smoking.<sup>47</sup> This combination markedly increased the product of the heart rate and systemic arterial pressure, a value that determines myocardial oxygen demand, while simultaneously decreasing the diameter of diseased segments of the coronary arteries.

The results of a recent survey suggest that 9 million people in the United States abuse cocaine and ethanol simultaneously.<sup>48</sup> Among those with abuse of multiple substances who are seen in emergency departments, the combination of cocaine and ethanol is the most common.<sup>1</sup> It is the second most common combination in patients who die of substance abuse, accounting for

more than 1000 deaths per year.<sup>49</sup> The concomitant use of cocaine and ethanol appears to be associated with higher rates of disability and death than either agent alone. Randall<sup>50</sup> reported that the simultaneous use of these substances increased the risk of sudden death by more than a factor of 20 in patients with postmortem evidence of coronary artery disease. Others<sup>51</sup> reported that patients who died of a combined overdose of cocaine and ethanol had much lower blood cocaine concentrations than those who died of an overdose of cocaine alone (900 and 2800 mg per liter, respectively), suggesting an additive or synergistic effect of ethanol on catastrophic cardiovascular events induced by cocaine.

Persons who abuse cocaine in temporal proximity to the ingestion of ethanol produce cocaethylene, a metabolite synthesized by hepatic transesterification. Like cocaine, it blocks the reuptake of dopamine at the synaptic cleft, thereby possibly potentiating the systemic toxic effects of cocaine.<sup>52</sup> At postmortem examination, cocaethylene is often detected in patients who died of cocaine and ethanol toxicity. In animals, cocaethylene is more lethal than cocaine.<sup>53</sup> In humans, the combination of cocaine and ethanol has been shown to cause increases in myocardial oxygen demand.<sup>54</sup>

#### COCAINE-INDUCED MYOCARDIAL DYSFUNCTION

Long-term cocaine abuse has been reported to cause left ventricular hypertrophy<sup>55</sup> and systolic dysfunction. Several reports have described dilated cardiomyopathy in long-term cocaine abusers, as well as reversible, profound myocardial depression after binge cocaine use.<sup>56-58</sup> Bertolet et al.<sup>57</sup> found evidence of left ventricular systolic dysfunction (by radionuclide ventriculography) in 7 percent of asymptomatic long-term cocaine users. These and other reports provide evidence that repeated exposure to cocaine may induce left ventricular systolic dysfunction.

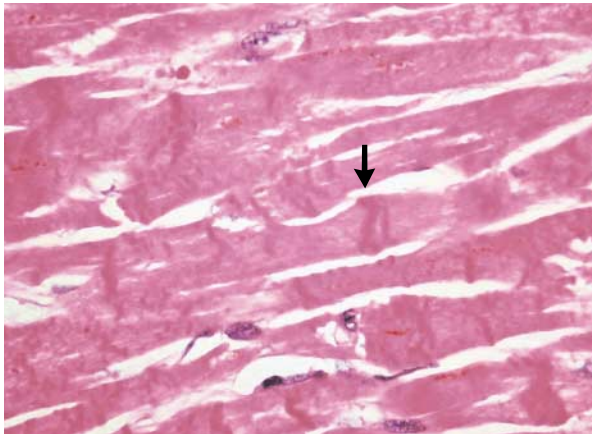
Cocaine may adversely affect left ventricular systolic function by means of several mechanisms. First, as described previously, cocaine may induce myocardial ischemia or infarction. Second, the profound repetitive sympathetic stimulation induced by cocaine is similar to that observed in patients with pheochromocytoma; both are associated with cardiomyopathy and characteristic microscopic changes of subendocardial contraction band necrosis (Fig. 3).<sup>59</sup> Third, the concomitant administration of adulterants or infectious agents may cause myocarditis, which has been seen on occasion in postmortem studies of intravenous cocaine users.<sup>26,60</sup> Fourth, studies in animals have shown that cocaine alters cytokine production in the endothelium and in circulating leukocytes,<sup>61</sup> induces the transcription of genes responsible for changes in the composition of myocardial collagen and myosin,<sup>62</sup> and induces myocyte apoptosis.<sup>63</sup>

Aside from the effects of long-term cocaine use

on myocardial performance, it may cause an acute deterioration of left ventricular systolic and diastolic function.<sup>64</sup> In some patients, this deterioration may be caused by metabolic disturbances, acid–base disturbances, or both that accompany cocaine intoxication, whereas in others it may be caused by a direct toxic effect of the drug. Pitts et al.<sup>64</sup> demonstrated that an intracoronary infusion of cocaine (in an amount sufficient to yield a concentration in coronary-sinus blood similar in magnitude to the peripheral-blood concentration found in abusers who have died of cocaine intoxication) had a deleterious effect on left ventricular systolic and diastolic function. A possible mechanism for these effects is that cocaine or its metabolites alter the manner in which myocytes handle calcium.<sup>65–67</sup>

### COCAINE-INDUCED DYSRHYTHMIAS

The cardiac dysrhythmias that may occur with cocaine use are listed in Table 3, but the precise arrhythmogenic potential of the drug is poorly defined. Electrophysiologic studies assessing its effects in humans are limited,<sup>68</sup> and there are no data available on the effects of the administration of large amounts of the drug. In many instances, the cardiac dysrhythmias ascribed to cocaine have occurred in the context of profound hemodynamic or metabolic derangements, such as hypotension, hypoxemia, seizures, or myocardial infarction.<sup>69</sup> Nonetheless, because of cocaine's sodium-channel–blocking properties and its ability to induce an enhanced sympathetic state, it is considered likely to produce or exacerbate cardiac arrhythmias, particularly under certain pathologic conditions. The



**Figure 3.** Photomicrograph of Myocardium from the Left Ventricle Obtained on Postmortem Examination of a Cocaine Abuser with Severe Left Ventricular Systolic Dysfunction.

The dysfunction was presumably caused by sustained and repetitive sympathetic stimulation induced by cocaine (hematoxylin and eosin,  $\times 200$ ). Contraction-band necrosis is evident (arrow). Photomicrograph courtesy of Dennis Burns, M.D., Department of Pathology, University of Texas Southwestern Medical Center.

development of lethal arrhythmias with cocaine use may require a substrate of abnormal myocardium. In support of this theory, studies in animals have shown that cocaine precipitates ventricular arrhythmias and fibrillation in the presence — but not the absence — of myocardial ischemia.<sup>70</sup> In humans, life-threatening arrhythmias and sudden death caused by arrhythmia related to cocaine use occur most often in patients with myocardial ischemia or infarction or in those with nonischemic myocellular damage. Long-term cocaine use is associated with increased left ventricular mass and wall thickness, which is known to be a risk factor for ventricular dysrhythmias.<sup>55</sup> In some cocaine users, this may provide the substrate that facilitates the development of arrhythmias.

Cocaine may affect the generation and conduction of cardiac impulses by several mechanisms. First, as a sympathomimetic agent, it may increase ventricular irritability and lower the threshold for fibrillation.<sup>71</sup> Second, it inhibits the generation and conduction of the action potential (i.e., it prolongs the durations of the QRS and QT intervals) as a result of its sodium-channel–blocking effects.<sup>29,72,73</sup> In so doing, cocaine acts in a manner similar to that of a class I antiarrhythmic agent. Third, cocaine increases the intracellular calcium concentration, which may result in afterdepolarizations and triggered ventricular arrhythmias.<sup>74</sup> Fourth, it reduces vagal activity — a change that is manifested as a reduction in the variability of the heart rate — which potentiates cocaine's sympathomimetic effects.<sup>75</sup>

Patients with ventricular dysrhythmias and heart block resulting from cocaine use should receive standard therapy, including the treatment of ischemia (if present), the correction of metabolic disturbances (e.g., electrolyte abnormalities, hypoxemia, or acid–base disturbances), the administration of appropriate antiarrhythmic agents, and temporary pacing, if indicated. Several reports have described the treatment of cocaine-induced wide-complex tachycardia with the administration of sodium bicarbonate,<sup>69,73,76</sup> and lidocaine has been used safely in patients with cocaine-induced ventricular tachycardia or fibrillation.<sup>77</sup> Class IA antiarrhythmic drugs, such as quinidine, procainamide, and disopyramide, should be avoided, since they may exacerbate prolongation of the QRS and QT intervals and slow the metabolism of cocaine and its metabolites.<sup>78–80</sup>

### ENDOCARDITIS

The intravenous use of any illicit drug is associated with an increased risk of bacterial endocarditis. Although several illicit drugs may be administered intravenously, the use of cocaine appears to be a greater independent risk factor than the use of other drugs for the development of endocarditis.<sup>81</sup> The reason for this enhanced risk of endocarditis in cocaine users is unknown. The elevation of the heart rate and systemic

**TABLE 3. CARDIAC DYSRHYTHMIAS AND CONDUCTION DISTURBANCES REPORTED WITH COCAINE USE.**

Sinus tachycardia
Sinus bradycardia
Supraventricular tachycardia
Bundle-branch block
Complete heart block
Accelerated idioventricular rhythm
Ventricular tachycardia
Ventricular fibrillation
Asystole
Torsade de pointes
Brugada pattern (right bundle-branch block with ST-segment elevation in leads V <sub>1</sub> , V <sub>2</sub> , and V <sub>3</sub> )

arterial pressure that accompanies cocaine use may induce valvular and vascular injury that predisposes users to bacterial invasion. The immunosuppressive effects of cocaine<sup>61</sup> may increase the risk of infection. Alternatively, the manner in which cocaine is manufactured, as well as the adulterants that are often present in cocaine, may increase the risk of endocarditis. In contrast to endocarditis associated with other drugs, the endocarditis associated with cocaine abuse more often involves the left-sided cardiac valves.<sup>81</sup>

**AORTIC DISSECTION**

Aortic dissection or rupture has been temporally related to cocaine use and should therefore be considered as a possible cause of chest pain in cocaine users.<sup>82-84</sup> Dissection probably results from the substantial increase in systemic arterial pressure induced by cocaine. In addition to aortic rupture, the cocaine-related rupture of mycotic and intracerebral aneurysms has been reported.<sup>85-87</sup>

**CONCLUSIONS**

Cocaine use continues to increase. As a result, the number of cocaine-related visits to emergency departments, hospitalizations, cardiovascular complications, and deaths has risen dramatically. The understanding and early recognition of cocaine-related cardiovascular complications are essential to their proper management. The possibility of cocaine use should be considered in young patients with myocardial ischemia or infarction, arrhythmias, myocarditis, or dilated cardiomyopathy.

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