Case Studies in Secondary Hypertension: Pheochromocytoma and Cocaine Intoxication

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Cover Illustration by Andrew Grivas
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Karen M. Warburton, MD

INTRODUCTION

Hypertension affects 50 million persons in the United States and approximately 1 billion persons worldwide. While essential, or idiopathic, hypertension accounts for the majority of cases, up to 5% of patients with hypertension have an identifiable cause that is potentially reversible. The differential diagnosis of secondary hypertension is broad and includes medications, endocrinopathies, and other systemic diseases. The presence of any of the following factors should lead one to suspect a diagnosis of secondary hypertension and to pursue additional diagnostic procedures:

- Proven age of onset of hypertension less than 20 years or greater than 50 years
- Negative family history for hypertension
- Resistance to antihypertensive medications
- Worsening of blood pressure control in a previously stable hypertensive patient
- Stage 3 hypertension or significant target organ damage
- Symptoms or physical examination findings suggestive of a secondary cause

This manual reviews diagnostic and treatment considerations for 2 important clinical scenarios in the complex field of secondary hypertension: pheochromocytoma and hypertension associated with cocaine use.

PHEOCHROMOCYTOMA

CASE PRESENTATION

A 48-year-old man with a 1 1/2-year history of refractory hypertension as well as occasional symptoms of “panic attacks” is referred to a hypertension clinic.

HISTORY AND PHYSICAL EXAMINATION

The patient is otherwise healthy but notes occasional “spells” of pounding headache and palpitations that occur suddenly and unpredictably. Blood pressure readings at his physician’s office have ranged from 140/85 mm Hg on first reading to 190/110 mm Hg when the reading is taken a minute or so later. He is currently taking atenolol 25 mg and lisinopril 5 mg, both daily. He tried several other blood pressure medications but had a variety of side effects from most of them. He is a nonsmoker and drinks 1 vodka and tonic each evening. His family history is significant for hypertension in 2 first-degree relatives.

On physical examination, his weight is stable at 180 lb. Blood pressure is 170/95 mm Hg in both arms with a pulse of 64 bpm. Funduscopic examination reveals mild arteriolar narrowing (grade I). Thyroid, chest, and cardiovascular examinations are normal, with no abdominal bruits and no lower extremity edema. Serum creatinine and electrolytes are within normal limits.

LABORATORY TESTING RESULTS

Because of the patient’s difficult-to-control hypertension and his hyperadrenergic symptoms, the primary care physician was concerned about the possibility of a pheochromocytoma and ordered a 24-hour collection for urine catecholamines. The results are as follows:

- Vanillylmandelic acid (VMA), 9.8 mg (normal, ≤ 6 mg)
- Metanephrine, 169 µg (normal, 45–290 µg)
- Normetanephrine, 2807 µg (normal, 85–500 µg)
- Epinephrine, 14 µg (normal, 2–24 µg)
- Norepinephrine, 784 µg (normal, 15–100 µg)

DIFFERENTIAL DIAGNOSIS

This patient likely has a secondary form of hypertension as evidenced by his resistance to antihypertensive medications, confirmation of target organ damage within 2 years of diagnosis, and symptoms suggestive of catecholamine excess. The triad of hypertension, hyperadrenergic symptoms, and elevated catecholamines, however, is not unique to pheochromocytoma. The challenge...
often is to distinguish between patients with pheochromocytoma and modest levels of catecholamine excess and those with secondarily activated sympathetic nervous systems who do not have pheochromocytoma.

There are several clinical situations in which one can see symptoms suggestive of sympathetic overactivity in the setting of difficult-to-control hypertension, including essential hypertension. Particularly in younger patients, essential hypertension has been associated with labile blood pressures, paroxysms of hypertension, and symptoms of adrenergic excess, such as palpitations, sweating, tachycardia, and anxiety. Occasionally, mild elevations of urinary catecholamines are also seen. Adrenergic symptoms may be seen with renovascular disease and hyperthyroidism, but neither is thought to lead to increased urine catecholamine levels.

Certain sympathomimetic drugs may mimick pheochromocytoma by causing severe hypertension, adrenergic symptoms and, occasionally, elevations in catecholamines. These include cocaine, amphetamines, the combination of tyramine-containing foods and a monoamine oxidase inhibitor; and, rarely, high-dose phenylpropanolamine used in over-the-counter decongestants and appetite suppressants. Alternatively, the abrupt withdrawal of short-acting sympathetic antagonists (eg, clonidine), which cause up-regulation of sympathetic receptors during sympathetic blockade, can produce a similar presentation. Likewise, withdrawal from alcohol mimics the scenario in this patient.

Less common causes of severe hypertension, adrenergic symptoms, and elevated urinary catecholamines include baroreceptor dysfunction, dystautonomia, intracranial lesions, and diencephalic "seizures." Pseudopheochromocytoma, a rare and poorly understood condition, refers to paroxysmal hypertension and adrenergic spells without an obvious cause. Patients with this condition often have episodes of severe hypertension associated with such symptoms as tachycardia, headache, chest pain, nausea, and palpitations. Catecholamine levels may be mildly elevated during attacks but between episodes are normal, as is blood pressure. Although most patients deny association between symptoms and stress or panic, this condition often responds to an antidepressant. True panic disorder, in contrast, is rarely associated with hypertension and is not associated with elevated catecholamines. While this patient has risk factors for essential hypertension, the elevations in his urinary catecholamines are well beyond those typically seen with essential hypertension. The triad of symptoms in this patient suggests an autonomous source of catecholamine production. In adults, the most common causes of these findings are pheochromocytoma and paraganglioma.

- What is the typical clinical presentation of pheochromocytoma?

**CLINICAL PRESENTATION**

The classic triad of symptoms seen in pheochromocytoma includes a pounding headache, palpitations or tachycardia, and diaphoresis. Although the complete triad is unusual, most people have 2 of the symptoms, which vary among patients but tend to be stereotypical for each individual. Symptoms are episodic, lasting 10 to 60 minutes, and range in frequency from daily in some patients to as infrequently as several times per year. Between 80% and 90% of patients with pheochromocytoma have hypertension, and for the majority of them the hypertension is sustained. Up to two thirds of patients with hypertension who have pheochromocytoma may have paroxysmal elevations in blood pressure. Hypertension in these patients is a complex process influenced by circulating catecholamines, the sympathetic nervous system, and alterations in the cardiovascular response to catecholamines.

Most pheochromocytomas are solitary benign adrenocortical tumors seen in adults between 20 and 50 years of age and are curable by surgical resection. Indeed, the frequently described "rule of 10s" illustrates the exceptions to their typical presentation (Table 1). These tumors were thought to be sporadic in 90% of cases, with the remainder attributed to a hereditary form of the disease. This statistic has been called into question as a result of recent data on the genetic basis for pheochromocytoma. It is likely that cases of familial pheochromocytoma that previously would have gone unrecognized are now being detected with increasing frequency due to the discovery of additional genes in the succinate dehydrogenase family associated with hereditary paragangliomas. Furthermore, understanding of how mutations in NF1, RET, and VHL predispose to formation of pheochromocytoma has also shed light on the genetic basis of these diseases. Although routine testing is low-yield in non-syndromic cases, current recommendations suggest that genetic testing should be considered in patients with a positive family history, young age at diagnosis, or the presence of extraadrenal or multifocal disease.

- What are the best tests for confirming states of catecholamine excess?

**APPROACH TO DIAGNOSIS**

The most sensitive test available for detecting pheochromocytoma is measurement of plasma free metanephrines. A normal result on this test virtually excludes all but the smallest pheochromocytomas (< 1 cm).
Normetanephrine and metanephrine, the O-methylated metabolites of norepinephrine and epinephrine, respectively, are formed continuously within tumor cells and released independently of their parent catecholamines. Theoretically, they are not affected by secondary stimulation of the sympathoadrenal system. Free (unconjugated) metanephrines are more representative of chromaffin-cell production, whereas levels of total (unconjugated) metanephrines are also affected by plasma clearance, making them unreliable in settings such as renal failure. A standard 24-hour collection for fractionated urine metanephrines, which integrates tumoral secretion over the collection period, will detect pheochromocytoma in the majority of cases, with a sensitivity ranging from 76% to 97%. It is important to document the adequacy of collection with a concomitant 24-hour urinary creatinine collection; otherwise, the metanephrine concentration may prove to be an underestimate. Both plasma and urine VMA, formerly the mainstay of diagnosis, have low negative predictive value when used alone. Ideally, these tests should be carried out after discontinuing medications known to increase catecholamines and their metabolites or interfere with the test itself, but doing so is not always practical. Tricyclic antidepressants primarily inhibit monoamine reuptake and block release of norepinephrine from sympathetic nerves. Phenoxycarbamide, a long-acting α-adrenergic-blocker that is often used to treat hypertension in the preoperative setting, should also be avoided until testing is complete. Selective α-adrenergic-blockers are an acceptable alternative. Other antihypertensives, with the possible exception of β-blockers, can be continued. Acetaminophen can directly interfere with assays of plasma free metanephrines and should also be avoided for 1 week prior to testing. Patients are also advised to avoid food, caffeine, and nicotine for several hours prior to testing.

In addition to the discontinuation of medications, the clonidine suppression test can be helpful in situations where pheochromocytoma is suspected but only moderate elevations of plasma metanephrines are demonstrated. Clonidine stimulates α2-adrenergic receptors in the brain as well as sympathetic nerve endings, thereby inhibiting norepinephrine release by sympathetic nerves. In an appropriate clinical setting, the inability of clonidine to produce a decrease in plasma norepinephrine by at least 50% suggests the presence of a pheochromocytoma.

Current recommendations are often highly dependent on institutional experience with certain methods. Figure 1 illustrates an algorithm for the biochemical diagnosis of pheochromocytoma, based on measurement of plasma free metanephrines as an initial test. At the University of Pennsylvania, the recommended workup includes a 24-hour urine collection for metanephrines and catecholamines to screen for suspected catecholamine-producing tumors. Further workup with imaging studies is undertaken if levels are elevated beyond 1.5 times the upper limit of normal. When values fall between the upper limit of normal and 1.5 times this amount, repeat testing of plasma free metanephrines is performed.

Table 1. Pheochromocytoma: Rule of 10s

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% of cases are diagnosed in children</td>
<td></td>
</tr>
<tr>
<td>10% are extracranial (&quot;paraganglioma&quot;), and of these cases 70%–80% are intraabdominal (abdominal sympathetic chain, urinary bladder)</td>
<td></td>
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<tr>
<td>10%–20% are intrathoracic (posterior mediastinum)</td>
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<tr>
<td>2% are head and neck (cervical sympathetic chain)</td>
<td></td>
</tr>
<tr>
<td>10% are multiple/bilateral</td>
<td></td>
</tr>
<tr>
<td>10% are familial*</td>
<td></td>
</tr>
<tr>
<td>Familial pheochromocytoma (autosomal dominant)</td>
<td></td>
</tr>
<tr>
<td>Syndromes associated with pheochromocytoma:</td>
<td></td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 2</td>
<td></td>
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<tr>
<td>von Hippel-Lindau Disease</td>
<td></td>
</tr>
<tr>
<td>Neurofibromatosis-1 (von Recklinghausen disease)</td>
<td></td>
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<tr>
<td>Hereditary paraganglioma</td>
<td></td>
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<tr>
<td>10% are malignant</td>
<td></td>
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<tr>
<td>10% recur after surgery</td>
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</tbody>
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10% are malignant
10% recur after surgery

*Probably an underestimate.
Figure 1. Algorithm for biochemical workup of suspected pheochromocytoma. CT = computed tomography; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging. (Adapted with permission from Eisenhofer G, Goldstein DS, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive results. J Clin Endocrinol Metab 2003;88:2656–66.)
its metabolite, normetanephrine. This finding and the patient’s difficult-to-control hypertension and adrenergic symptoms in the absence of another good explanation necessitate further workup for pheochromocytoma.

Imaging is appropriate in the workup for pheochromocytoma only after biochemical documentation of catecholamine excess has been demonstrated. Sensitivities for detection of an adrenal mass are similar for computed tomography (CT) scanning and magnetic resonance imaging (MRI) (93%–100%); however, MRI is often preferred because pheochromocytomas tend to be particularly bright on T2-weighted images, which increases the otherwise poor specificity of this imaging test.

If the result of MRI is negative for adrenal mass and suspicion is high enough, imaging to look for a paraganglioma may be appropriate. When detecting extra-adrenal tumors, MRI is more sensitive than CT scanning. An additional option is an MIBG test to look for uptake in a nonadrenal location. MIBG involves scintigraphic localization with 1-metaiodobenzylguanidine, which preferentially accumulates in catecholamine-producing tumors. Although very specific (95%–100%), this test is not sensitive enough to exclude pheochromocytoma (sensitivity, 77%–90%). Positron-emission tomography scanning, if available, is used when conventional imaging fails to identify a tumor site in a patient with a markedly abnormal biochemical profile.

**IMAGING RESULTS**

The case patient undergoes MRI, which reveals a 3-cm left adrenal mass.

- **What is the management of pheochromocytoma?**
  - **Prognosis?**

**MANAGEMENT AND PROGNOSIS**

The mainstay of therapy for pheochromocytoma is surgical resection. Most tumors are benign and can be completely excised. Preoperative preparation with adrenergic blockade has substantially decreased surgical mortality. Phenoxybenzamine is commonly used at doses of 10 to 20 mg twice daily for at least 1 week up until surgery. Given phenoxybenzamine’s effect on testing, this medication should be held until biochemical documentation of catecholamine excess has been established. Angiotensin-converting enzyme (ACE) inhibitors and calcium-channel blockers can be used as adjuvant therapy. Intraoperative hypertensive crises can be managed with nitroprusside, nitroglycerin, phenolamine, or labetalol. β-Blockers, which can be helpful in the management of tachycardia and arrhythmias, should never be given without first creating α blockade. If β-blockers are indicated, a cardioselective β1-blocker such as metoprolol is preferable. α-Methyl tyrosine, a tyrosine-hydroxylase inhibitor that limits tachycardia and hypertension, may be useful in the week prior to surgery. It is important to achieve tight blood pressure control in preparation for surgery, and patients should be encouraged either to purchase a home blood pressure monitor or to have their blood pressure checked frequently in the interim.

Hypertension is cured in the majority of patients after surgery. Blood pressure is typically normal by discharge from the hospital, but some patients have hypertension up to 2 months postoperatively. Persistently elevated blood pressure beyond 2 months may suggest resetting of baroreceptors, established hemodynamic changes, functional or structural changes in the kidney or, more commonly, coincident essential hypertension that has been previously undiagnosed.

Urinary catecholamine measurements may remain elevated postoperatively as residual catecholamine in other tissue may leach out for a period after surgery. Postoperative follow-up includes measurement of plasma metanephrine levels at approximately 3 to 6 weeks and again at 6 months after surgery. All patients who undergo resection of pheochromocytoma should have annual measurements of urinary catecholamines for at least 5 years postoperatively, or earlier if symptoms recur.

**CASE RESOLUTION**

After the patient’s pheochromocytoma is confirmed, his β-blocker is discontinued. He is started on phenoxybenzamine 10 mg orally twice daily, and this dose is titrated upward for normotension prior to surgery. Three weeks later, he undergoes resection of his adrenal tumor.

**COCAINE-INDUCED HYPERTENSION**

**CASE PRESENTATION**

A 24-year-old man is brought by police to the emergency department for unusual behavior following an altercation. He is very agitated and admits to smoking crack cocaine 3 hours prior to arrest. On presentation, he is hypertensive with a blood pressure of 180/100 mm Hg.

**HISTORY AND PHYSICAL EXAMINATION**

The patient has a known history of polysubstance abuse, including cocaine, alcohol, and tobacco. He smokes a pack of cigarettes per day, and although he has abstained from alcohol for 2 months, he admits to...
smoking crack approximately twice a week. He denies any other medical problems, including hypertension, diabetes mellitus, and heart disease, and he takes no prescription medications. Family history is negative for cardiovascular disease, including hypertension. Review of systems reveals no headache, changes in vision, chest pain, shortness of breath, or abdominal pain. On physical examination, the patient’s temperature is 99.1°F, pulse is 110 bpm and regular, blood pressure in both arms is 175/90 mm Hg, and oxygen saturation is 98% on room air. Funduscopic, cardiovascular, lung, and abdominal examinations are normal. Neuropsychiatric evaluation is significant for pressured speech and psychomotor agitation.

- **How common is cocaine use in the United States?**

  The incidence of nontherapeutic use of cocaine peaked in the mid-1980s but is again on the rise, perhaps reflecting the increased availability of the inexpensive, fast-acting freebase form known as crack. In 2000, the National Household Surveys on Drug Abuse reported that 25 million people admitted to using cocaine at some time, and 1.5 million people in the United States use it currently.23 Individuals commonly using cocaine are young males from 18 to 25 years of age. The cost of cocaine-related hospitalizations exceeds $80 million per year, yet the incidence of cocaine toxicity is likely to be grossly underreported. The increasing availability of more potent forms, such as intravenous and smoked cocaine, suggests that we can expect the burden on the health care system continue to increase.

  Even casual use can be associated with acute and chronic toxicity. In addition, it is not necessary to have underlying cardiovascular disease to experience serious side effects of cocaine use. In fact, significant risk factors, other than smoking, are rarely present.24

- **What are the physiologic effects of cocaine?**

  Cocaine is a powerful sympathomimetic agent that potentially affects any organ in the body. Cocaine blocks norepinephrine and dopamine reuptake into the synaptic cleft by sympathetic neurons, stimulates release of catecholamines from central and peripheral stores, and at the cellular level enhances α- and β-receptor sensitivity. Cocaine is also believed to block serotonin reuptake, although the significance of this effect with regard to cardiovascular side effects is unknown.25 Following the administration of cocaine, patients typically experience a dose-dependent increase in blood pressure and heart rate that in recreational doses is usually modest. Many patients also complain of chest pain, shortness of breath, anxiety, palpitations, dizziness, and nausea, all symptoms that mimic the acute coronary syndrome. Accordingly, the pathophysiology of cocaine intoxication is best studied with regard to the heart. Although only 6% of patients presenting with cocaine-associated chest pain are found to have an acute MI, the risk of MI is increased 24-fold in the hour following cocaine use.26,27

  Cocaine’s effects on the heart are extremely complex and remain incompletely understood, despite being the most well-studied facet of cocaine intoxication. Acutely, there may be a demand and supply mismatch: increased heart rate, systolic arterial pressure, and left ventricular contractility create increased myocardial oxygen demand, but coronary arterial vasoconstriction inappropriately decreases supply. In addition, cocaine is thought to induce platelet aggregation, in situ thrombus formation, and decreased fibrinolysis.25,26

  Chronic use of cocaine is thought to induce structural changes in endothelial cells, leading to accelerated atherosclerosis. The repetitive sympathetic stimulation caused by chronic cocaine use may cause structural changes in the myocardium similar to those seen in other states of sympathoadrenal hyperactivity such as pheochromocytoma. This diffuse, typically non-ischemic, cardiomyopathy probably occurs due to activation of α1-adrenergic receptors and/or enhanced calcium entry into cells. On echocardiogram, these patients often demonstrate left ventricular hypertrophy, and in some there is dilated cardiomyopathy.28

  Although neurologic complications include hemorrhagic and thromboembolic strokes and seizures, patients more commonly present with varying degrees of anxiety and agitation and/or hyperthermia. As is true with cardiac disease and cocaine, most patients who develop neurologic side effects of cocaine do not have underlying cerebrovascular disease. Other side effects of cocaine include arrhythmias, rhabdomyolysis, acute mesenteric ischemia, obstetric and neonatal emergencies, thromboembolic events, infections (particularly with intravenous use), and numerous pulmonary side effects that depend largely on the route of use.

- **What is the initial approach to managing a patient with acute cocaine intoxication?**

**INITIAL WORKUP FOR COCAINE INTOXICATION**

An initial workup of cocaine-induced hypertension should seek evidence of end-organ damage. It is important to ask about headache, blurry vision, shortness of breath, chest pain, and abdominal and flank pain. Physical examination should include a thorough funduscopic examination to rule out papilledema, hemorrhage, and/or exudates. Laboratory workup should
evaluate renal function, assess for proteinuria and hematuria, and rule out a microangiopathic process. While it is important to assess for MI, traditional means of diagnosing the acute coronary syndrome are often misleading in patients with cocaine intoxication. The electrocardiogram (ECG) is less sensitive in that it can be normal even in the setting of acute ischemia, and is less specific because cocaine users often have ST segment elevations attributable to repolarization abnormalities that can be misread as acute ischemia. In addition, elevations in cardiac enzymes are often attributable to rhabdomyolysis rather than cardiac ischemia. Catastrophic complications such as aortic dissection, typically in the setting of severe hypertension, must also be considered.

LABORATORY TESTING RESULTS

The patient’s serum creatinine on presentation is 1.0 mg/dL. Urinalysis reveals no proteinuria or hematuria. Creatine kinase is elevated at 1250 mg/dL with a normal relative index and normal troponin I level. The ECG is significant for sinus tachycardia and signs of left ventricular hypertrophy.

- What is the association between cocaine use and acute hypertension?

COCAINE USE AND HYPERTENSION

A recreational dose of cocaine typically increases the heart rate by approximately 30 bpm and increases blood pressure by 20–30/10–20 mm Hg. These effects are modest and equivalent to mild exercise. Approximately one third of patients who present with acute cocaine intoxication have elevated blood pressure; in most of them, this effect is transient and does not lead to end-organ damage.

Though typically associated with mild and self-limited acute elevations in blood pressure, cocaine has been implicated in cases of accelerated and malignant hypertension. Case reports of at least 2 African American patients who both had a history of prior hypertension were thought to have accelerated hypertension, presenting with elevations in diastolic blood pressure over 130 mm Hg, funduscopic changes, renal insufficiency, proteinuria, and normal-sized kidneys on ultrasound. Renal biopsies revealed fibrinoid necrosis involving the small interlobular arterioles with significant intimal proliferation, mimicking the pathologic findings often seen in scleroderma renal crisis. The mechanism for this accelerated form of hypertension was thought to be an extension of cocaine’s sympathomimetic effects on vasoconstriction. Predisposing factors in these patients included race, prior history of hypertension, and use of crack cocaine, a more potent form of the drug. African Americans are more likely than white patients to develop end-stage renal disease from hypertension and perhaps are more susceptible to the hypertensive action of cocaine. Because African Americans tend to have a greater degree of vascular disease and renal vascular resistance than whites, as well as more nephrosclerosis, they may be more susceptible to the vasoconstrictive properties of cocaine.

- What is the association between cocaine and chronic hypertension?

Although the association between cocaine and acute elevations in blood pressure is well established, only a few studies have addressed the question of whether the use of cocaine leads to chronic hypertension in the absence of chronic kidney disease.

One study looking at a group of predominately black men with normal renal function who used cocaine as well as other substances (particularly ethanol, which is known to elevate blood pressure) found that 18% had chronic elevations in blood pressure greater than 140/90 mm Hg. When compared with a predominately black population from the NHANES III data, however, there was no increase in blood pressure in the cocaine users. The CARDIA study followed a cohort of cocaine-abusing individuals for 7 years and noted a stable prevalence of hypertension over the duration of the study, suggesting that the cardiovascular toxicities of cocaine may be limited to its acute effects. In general, studies such as these have been limited by the difficulty of isolating cocaine use as an independent risk factor for hypertension in these patients, many of whom also smoke cigarettes, drink alcohol, abuse other recreational drugs, and have renal disease. It has been suggested that cocaine may alter the vasculature and lay the groundwork for hypertension later in life, but at this time an isolated increased risk of long-term hypertension from chronic cocaine use has not been firmly demonstrated.

- What are the effects of cocaine on the kidney?

Other than the known side effect of acute tubular necrosis secondary to rhabdomyolysis, little is known about the relationship between cocaine and acute renal failure. As discussed earlier, cocaine may cause malignant hypertension and thereby precipitate acute renal failure. Cocaine has also been implicated in cases of renal infarction, but the mechanisms of these events are not completely understood. Women who use cocaine in pregnancy may develop pregnancy-related acute renal failure that is clinically similar to preeclampsia. Rarely, cocaine has been associated with interstitial nephritis and antglomerular basement membrane disease.
Cocaine traditionally has not been thought to cause chronic kidney disease, although recent data suggest that chronic use may lead to a chronic, insidious form of renal failure, the etiology of which is likely multifactorial. One study of patients with hypertensive end-stage renal disease on hemodialysis in an inner-city community demonstrated a close relationship between history of cocaine use and progression of preexisting renal disease. While cocaine may have a direct effect on worsening kidney function, other potential mechanisms, such as antihypertensive noncompliance, makes it difficult to prove that cocaine independently causes progression of renal disease.

Based on data regarding cocaine’s effects on the heart, we know that it causes potent vasoconstriction of vascular smooth muscle, small-vessel ischemia, and accelerated atherosclerosis. This concept may also apply to the kidney. Proposed mechanisms for renal disease in chronic cocaine use include hemodynamic effects such as vasoconstriction of vascular smooth muscle leading to ischemic nephropathy and secondary hypertension; interactions between endothelin-1, the nitric oxide pathway, and the renin-angiotensin system; effects on glomerular matrix synthesis and degradation, leading to oxidative stress and secondary activation of the renin-angiotensin system; and accelerated atherogenesis. In addition, chronic cocaine use may accelerate hypertensive nephrosclerosis in susceptible populations.

In summary, cocaine is associated with progression of hypertensive renal disease in certain susceptible populations by mechanisms that are incompletely understood and likely multifactorial.

- **When is it necessary to treat a patient with cocaine-induced hypertension?**

**TREATMENT OF COCAINE INTOXICATION**

The knowledge that patients who present with hypertensive crisis are also at increased risk for cocaine-induced MI, stroke, seizure, and acute renal failure should guide the approach to therapy of cocaine-induced hypertension. Initial management, in addition to addressing airway and breathing, should focus on close monitoring of cardiac, neurologic, and renal function, as uncontrolled hypertension can damage vascular endothelium, resulting in pulmonary and cerebral edema, hemorrhage, or infarct.

Cocaine has a half-life of 30 to 90 minutes. The peak effect occurs within 1 hour of use, during which most complications are seen. Occasionally, patients experience delayed symptoms that are probably due to cocaine’s major metabolites, leading to vasoconstriction of the coronary arteries several hours after ingestion. The pharmacokinetics differ slightly depending on the form of cocaine ingested. For example, cocaine hydrochloride, the water-soluble salt that is used intranasally or intravenously, has an onset time of 1 to 5 minutes. In contrast, “crack,” prepared from cocaine hydrochloride by organic extraction with ether into the basic, nonsalt form, is typically smoked and has an onset of action within seconds, a peak effect of less than 1 minute, and a duration of action that is often less than 30 minutes.

The case patient presented above has elevated blood pressure in the setting of recent crack cocaine use without evidence of end-organ damage. For the reasons discussed above, he probably does not require aggressive pharmacologic blood pressure lowering in the emergency department as the form of cocaine that he has used has a short half-life and should wear off quickly. Cardiac effects are often short-lived, and most patients with cocaine intoxication, even with tachycardia and hypertension, can be treated with conservative, nonpharmacologic therapy. It is rarely necessary to treat hypertension in the absence of evidence of end-organ damage such as MI, stroke, pulmonary edema, encephalopathy, or acute renal failure. The psychomotor agitation, even if untreated, should resolve within 30 to 40 minutes after use of crack cocaine.

**SECOND PATIENT PRESENTATION**

The patient returns to the emergency department 3 weeks later following another crack smoking binge. This time, blood pressure is 220/135 mm Hg. Funduscopic examination reveals evidence of cotton-wool spots. He complains of shortness of breath, and physical examination reveals jugular venous distension, bibasilar rales, and 1+ pitting edema in both lower extremities. Urinalysis is notable for 1+ protein and no blood. Serum creatinine is 2.0 mg/dL. Chest radiograph reveals mild pulmonary edema, and ECG again shows left ventricular hypertrophy. Urine is positive for cocaine.

This presentation is concerning for accelerated hypertension, and the patient must now be treated with pharmacologic therapy.

- **What pharmacologic agents are used to treat a patient with cocaine-induced hypertension?**

Most recommendations regarding management of cocaine-associated hypertension come from well-designed animal trials, observational studies, or case series. Few, if any, address management of hypertension in isolation from the acute coronary syndrome or stroke. The general approach to treatment of cocaine-induced hypertension is summarized in Table 2.
Most patients with cocaine-induced hypertension, in the absence of stroke or acute coronary syndrome, can be managed successfully with benzodiazepines alone. As demonstrated primarily in animal studies, management of the central (neuropsychiatric) manifestations associated with cocaine intoxication will often lead to resolution of the peripheral (cardiovascular) complications. Benzodiazepines blunt increases in sympathetic tone, in part through their anxiolytic effects as γ-aminobutyric acid agonists, thereby reducing blood pressure, heart rate, and myocardial oxygen demand.24 They should be considered first-line agents for patients who are hypertensive, tachycardic, anxious, or combative.24,33,36,37 For patients in whom benzodiazepines are not effective, other options include ACE inhibitors, nitrates, α-adrenergic blockers, and, potentially, calcium-channel blockers. ACE inhibitors, which have also been advocated as first-line therapy for cocaine-related hypertensive urgency, are thought to have a role in resetting the cerebral autoregulatory curve to a lower level, reducing sympathetic overactivity and may even improve survival in patients with hypertensive encephalopathy.38–40 There are not yet data on angiotensin-receptor blockers in the management of cocaine-associated hypertension.

Nitrates have been shown to reverse cocaine-induced coronary artery vasoconstriction in humans and have a class I indication in the management of cocaine-associated acute coronary syndrome, although no randomized controlled trials have tested these observations. They are likely a safe and effective second-line treatment option for cocaine-associated hypertension.36,37,41 α-Adrenergic receptors treat many of the hemodynamic effects of cocaine. The α-blocker phentolamine

### Table 2. Treatment of Cocaine-Induced Hypertensive Urgency/Emergency

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agent and Dose</th>
<th>Potential Mechanism</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Lorazepam 2–4 mg IV</td>
<td>GABA agonist, anxiolytic, blunt increases in sympathetic tone</td>
<td>First-line</td>
</tr>
<tr>
<td></td>
<td>Diazepam 5–10 mg IV (repeat as needed)</td>
<td></td>
<td></td>
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<tr>
<td>ACE inhibitors</td>
<td>Enalaprilat 0.625mg IV, 0.625–5 mg every 6 hours as needed</td>
<td>Reset cerebral autoregulatory curve, reduce sympathetic overactivity</td>
<td>First-line Note: no data yet on ARB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Manage CHF</td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>IV nitroglycerin 10 µg/min starting dose</td>
<td>Arterial (nipride) and venodilator (nipride, nitroglycerin)</td>
<td>Second-line agent</td>
</tr>
<tr>
<td></td>
<td>IV nitroprusside 0.25–0.5 µg/kg/min (titrate to effect)</td>
<td>Coronary vasodilator</td>
<td>First-line in acute coronary syndrome</td>
</tr>
<tr>
<td>α-Blocker</td>
<td>Phentolamine 1 mg IV every 5–15 min</td>
<td>Antagonism of circulating catecholamines</td>
<td>Second-line agent</td>
</tr>
<tr>
<td>Calcium-channel</td>
<td>Verapamil 10 mg IV over 2 min (repeat as needed)</td>
<td>Block adrenergically mediated vasoconstriction via calcium-dependent catecholamine release from presynaptic terminals</td>
<td>Verapamil is second- or third-line agent, only after benzodiazepines have been given for neuroprotection Note: Dihydropyridine is not yet studied in humans</td>
</tr>
<tr>
<td>blocker</td>
<td></td>
<td>Coronary vasodilator</td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>Propranolol</td>
<td>Coronary artery vasoconstrictor</td>
<td>Contraindicated</td>
</tr>
<tr>
<td></td>
<td>Esmolol</td>
<td>Paradoxical hypertension</td>
<td></td>
</tr>
<tr>
<td>Combined α- and β-blocker</td>
<td>Labetalol</td>
<td>No improvement in coronary vasoconstriction Potential risks of β-blockers as above</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CHF = congestive heart failure; GABA = γ-aminobutyric acid; IV = intravenous.
has been shown to reduce blood pressure and heart rate as well as act as a coronary vasodilator in humans with cocaine intoxication; it is recommended as second-line therapy for benzodiazepine-refractory patients with cocaine-associated acute coronary syndrome.\textsuperscript{37,42,43} \(\alpha\)-Blockers are also anecdotally recommended as second-line therapy for cocaine-related hypertension that is unresponsive to benzodiazepines. Data also show that calcium-channel blockers may have a role in the management of cocaine-associated cardiovascular complications, including human studies showing that intravenous verapamil reverses cardiac ischemia caused by cocaine-induced vasoconstriction.\textsuperscript{34} These should be given only after benzodiazepines have been administered in order to protect the central nervous system.

\(\beta\)-Blockers had been considered first-line therapy in the use of acute cocaine intoxication, but there is now an overwhelming consensus based on combined data from animal and human studies that \(\beta\)-blockers are neither safe nor effective in the management of patients with acute cocaine-related complications.\textsuperscript{24,26,37,45,46} Human data suggest that \(\beta\)-blockers induce vasoconstriction of the coronary arteries and cause a paradoxical exacerbation of hypertension.\textsuperscript{45} This problem is particularly pertinent to nonselective \(\beta\)-blockers (eg, propranolol) that block the \(\beta_2\)-receptors, producing unopposed \(\alpha\)-receptor stimulation in the peripheral vasculature and often worsen blood pressure control. This paradoxical rise in blood pressure was also shown in humans treated with intravenous esmolol, seemingly an ideal drug for treating cardiac manifestations of cocaine intoxication because of its short half-life.\textsuperscript{46} Even labetalol, a combined \(\alpha\)- and \(\beta\)-blocker, has not been found to improve ischemia in humans with coronary vasoconstriction due to cocaine use and thus is not recommended for cocaine-related hypertensive crisis.\textsuperscript{45,47}

In contrast to the management of most other causes of hypertensive urgency or emergency, hypertension associated with cocaine is typically acute and can be treated as such. If the decision is made to treat, it is usually acceptable to lower the blood pressure to normal (baseline) quickly. An exception would be the patient with known long-standing hypertension who is at risk of cerebral hypoperfusion should the blood pressure be lowered too quickly.

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**References**


