pH-Dependent Cocaine-Induced Cardiotoxicity

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Severe cocaine toxicity causes acidemia and cardiac dysfunction. These manifestations are described in 4 patients who presented with seizures, psychomotor agitation, and cardiopulmonary arrest. Their initial laboratory values demonstrated acidemia and electrocardiographic findings that included a prolonged QRS complex and QTc duration and a rightward T40 ms axis deviation. Treatment of the patients with hyperventilation, sedation, active cooling, and sodium bicarbonate infusion led to the normalization of their blood pHs and reversal of their cardiac conduction disorders. Acidemia can contribute to cocaine cardiac disorders by promoting conduction delays, dysrhythmias, and depressed myocardial contractility. Good supportive care corrects the blood pH and cardiac conduction disorders and remains the major focus in the management of patients with cocaine toxicity. (Am J Emerg Med 1999;17:364-369. Copyright © 1999 by W.B. Saunders Company)

The annual use of cocaine in this country from 1991 to 1994 has declined from 2.5% to 1.3%, whereas the number of regular users stayed relatively constant at about 1.5 million.[1] Emergency department (ED) visits related to cocaine, however, rose by 78% in these years.[2] Between the first half of 1995 and that of 1996, this number was about 70,000.[2] Despite the decrease in cocaine use by the general population, the use of this substance is still associated with significant morbidity and mortality. The incidence of deaths related to cocaine increased by 14% from 1992 to 1995.[3] In 1995, cocaine was the most frequent drug reported to the medical examiner for drug abuse deaths.[3]

The medical complications of cocaine toxicity are several, and they include cerebrovascular accidents, seizures, limb ischemia, myocardial infarction, and sudden death. The incidence of fatal cocaine toxicity continues to increase in the last decade.[3] Sudden death is usually caused by a cardiac dysrhythmia.[4,5] Because the majority of these patients do not arrive at the hospital alive, information regarding the clinical evolution of this event and treatment is limited.[6,7] It is important for health care providers to treat survivors appropriately. This report describes a series of patients with acute cocaine toxicity with severe acidemia and cardiac conduction disorders that promptly resolved with correction of the metabolic condition.

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CASE REPORTS

Case 1

A 43-year-old man was witnessed to administer a "large" dose of cocaine IV in a suicide attempt. The patient became lethargic, seized, and was brought immediately to the ED. Vital signs were blood pressure 170/80mmHg, pulse rate of 140 beats/min, respiratory rate of 10 breaths/min, and rectal temperature 100°F (37.7°C). He was lethargic, seized, and became asystolic. Resuscitation was successful after 13 minutes. Atropine, epinephrine, lidocaine, and pentobarbital were administered. Arterial blood gas (ABG) after resuscitation was pH 6.72, $PaCO_2$ 84mmHg, and PaO_2 115mmHg. The initial electrocardiogram (ECG) showed a wide complex tachycardia of an undetermined origin (Figure 1). Subsequent ECGs and arterial blood pHs are presented in Table 1. The patient's blood pH was maintained at 7.50 with a sodium bicarbonate infusion, and he was admitted to the intensive care unit. After 12 hours from the time of admission, the ECG remained normal and the bicarbonate infusion was discontinued. Comprehensive toxicology screen was positive only for cocaine and benzoylecgonine (BE). Urine BE was 18, 363 ng/mL.

Case 2

A 25-year-old man was resuscitated with epinephrine after arresting from the ingestion of one "knot" of crack cocaine (2.5 g), which was placed in a plastic resealable bag. His admitting vital signs in the ED were a blood pressure of 92/50mmHg, pulse rate of 139 beats/min, intubated, and a rectal temperature of 95.2°F (35.1°C). ECG#1 sinus rhythm, QRS duration 120msec, QTc 510msec, QRS axis 300°, terminal 40msec of the QRS (terminal (T) 40msec) axis 285°, with the following ABG: pH 6.92, $PaCO_2$ 58mmHg, PaO_2 83mmHg. After 100mEq $NaHCO_3$ IV, ECG#2 QRSD 100msec, QTc 490msec, QRS axis 15°, T40msec axis 30°, and a follow-up ABG, pH 7.30, $PaCO_2$ 38mmHg, PaO_2 430mmHg. Oral activated charcoal and whole bowel irrigation therapy with polyethylene glycol electrolyte lavage solution were begun for the ingestion, and the patient was admitted to the intensive care unit. A continuous infusion of lorazepam was used to manage persistent agitation. The patient passed per rectum the bag of cocaine within 12 hours of admission, and he was extubated at 48 hours. An upper gastrointestinal series and a small bowel follow-through were later performed and interpreted as normal.

Case 3

A 38-year-old man reportedly administered 500mg of "street-grade" cocaine intravenously and developed psychomotor agitation. Vital signs in the ED were a systolic blood pressure of 90mmHg, pulse rate of 132 beats/min, and a rectal temperature 109°F (43°C). The patient was sedated with benzodiazepines and intubated. ECG#1, sinus rhythm, QRSD 117msec, QTc 440msec, QRS axis 300°, T40msec axis 255°, (ABG, pH = 7.10, $PaCO_2$ 47mmHg, PaO_2 98mmHg, postintubation) (Figure 2A). Active cooling with an ice water bath and hydration with IV normal saline decreased the patient's body temperature to 101°F (38.4°C). The patient was admitted to the intensive care unit and received benzodiazepines for sedation. Sodium bicarbonate was not administered. At 7 hours after admission, ECG#2 QRSD 100msec, QTc

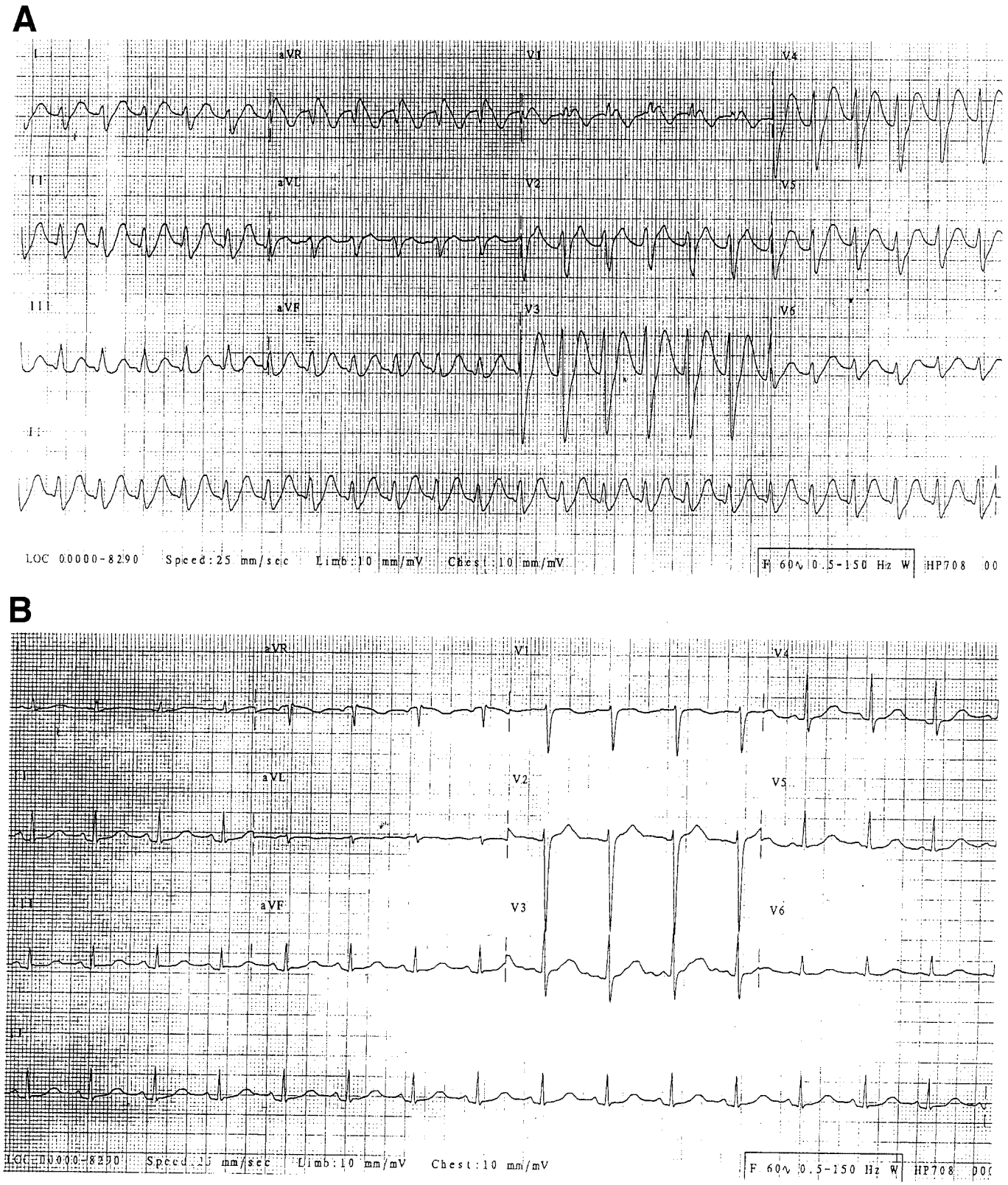

FIGURE 1. (A) Electrocardiogram of the patient in case 1, status after cocaine-related cardiac arrest. The arterial blood pH was 6.72. (B) Electrocardiogram of the patient in case 1 after the administration of 150 mEq sodium bicarbonate IV. The arterial blood pH was 7.40.

TABLE 1. Events after the Cardiopulmonary Arrest of the Patient in Case 1. Blood pH, ECG Changes and Bicarbonate Administered are Shown

Time	Arterial pH	QRSD (msec)	QTc (msec)	QRS Axis	T40msec* Axis	$NaHCO_3$ (mEq)
0	6.72	150	530	141°	255°	status post arrest
11min	6.79	146	449	176	225	100
25min	7.10	122	508	95	225	50
56min	7.40	78	473	76	165	50
337min	7.57	70	480	42	30	
2 days	7.41	74	389	42	30	

*Terminal 40 milliseconds of the QRS complex.

440msec, QRS axis 30°, T40msec axis 240°, (ABG, pH = 7.34, $PaCO_2$ 35mmHg, PaO_2 125mmHg, intubated) (Figure 2B). No interval ECG was performed since the initial one.

Case 4

A 20-year-old man presented to the ED with repeated seizures after ingesting 1/8 oz of "street-grade" cocaine. Initial vital signs were blood pressure 109mmHg by palpation, heart rate 110, and a rectal temperature of 101°F (38°C). The patient received benzodiazepines, barbiturates, and was intubated. ECG#1 sinus rhythm, QRSD 123msec, QTc 537msec, QRS axis 27°, T40msec axis 210°, (ABG, pH 6.77, PaO_2 347mmHg, $PaCO_2$ 102mmHg, FiO_2 100%). After hyperventilation, ECG#2 QRSD 93msec, QTc 432msec, QRS axis 22°, T40msec axis 210°, (ABG, pH 7.31, PaO_2 401mmHg, $PaCO_2$ 33mmHg). Sodium bicarbonate (50mEq) IV was then given. ECG#3 QRSD 87msec, QTc 434msec, QRS axis 13°, T40msec axis 135°, (ABG, pH 7.46, PaO_2 334mmHg, $PaCO_2$ 24mmHg). The patient was admitted to the intensive care unit and extubated at 48 hours.

For all patients: (+) urine BE, (−) tricyclic antidepressants, (−) creatine kinase MB band (CK-MB) for myocardial infarction. The admission serum potassium for the patients are shown in Table 2. All patients had a normal computer axial tomography scan of the brain and survived to discharge from the hospital.

DISCUSSION

The clinical manifestations of the above patients have been described for cocaine toxicity and consist of lethargy, seizures, psychomotor agitation, hyperthermia, dysrhythmias, and cardiopulmonary arrest. Cardiac conduction disorders, including prolonged QTc duration and ST segment and T-wave abnormalities, also have been observed to be more common in patients with acute toxicity.[8,9] However, the association between these electrocardiographic changes and acidemia in the clinical setting have been reported infrequently.[10,11]

A wide variety of cardiovascular disorders are related to cocaine use: they include myocardial ischemia, infarction, dysrhythmias, myocarditis, cardiomyopathies, hypertension, and sudden death.[12-15] Elevated catecholamine levels contribute to the pathophysiology of cocaine cardiac toxicity, which include systemic arterial hypertension, increased myocardial oxygen demand, and coronary vasospasm.[16] Dysrhythmias are the most likely cause of sudden death in this population.[5] The causes of rhythm disturbances in cocaine toxicity are unclear, although several possibilities exist. They include myocardial infarction, sympathomimetic stimulation, and direct local anesthetic and antimuscarinic effects on the heart.[17,18] Cardiac injury has not been supported as a cause because autopsies in cocaine-related deaths have shown few with evidence of acute infarction.[6,7]

Cocaine affects ion flow in the myocardium by several different mechanisms.[18,19] Alpha-adrenergic stimulation of the heart by cocaine can cause increased cytosolic calcium levels. Cocaine is classified as a type I antidysrhythmic (eg, quinidine) because of its ability to block potassium and sodium channels.[20] This latter effect results in a depression of depolarization, a slowing of conduction velocity, and a promotion of conduction blocks, which favors reentry excitation. On the ECG, this is noted as a prolongation of the PR duration, QRS complex and QTc interval.[21] The inhibition of outward potassium flow affects membrane potential during repolarization, which may predispose to dysrhythmias, as well. In isolated mammalian cardiac myocytes, cocaine was shown to block muscarinic-mediated potassium channels to raise membrane action potential threshold.[18] It would appear that these ionic effects alone would be enough to precipitate dysrhythmias. However, the administration of cocaine to animals caused infrequent ventricular and idioventricular rhythm disturbances.[22,23] Other factors are most likely involved in the generation of dysrhythmias in cocaine toxicity.

Experimental evidence clearly supports the deleterious effects of acidosis on cardiac function. Myocardial contractility is depressed when intracellular pH is lowered because of decreased calcium delivery to the myofilaments and responsiveness of the contractile proteins.[24] Acidosis potentiates dysrhythmias by causing repolarization and depolarization abnormalities that lead to reexcitation states. Calcium is spontaneously released from the sarcoplasmic reticulum when the pH falls, which establishes a transient depolarizing current.[25] This can precipitate dysrhythmias during periods of diastole.[26] Also, acidosis decreases the conductance between the gap junctions of cardiac cells, which slows the propagation of the action potential.[27] In the presence of an agent that diminishes sodium conductance (eg, type I antidysrhythmic), there would be a severe reduction in conduction velocity and an increased likelihood of dysrhythmias by reentry excitation. Thus, acidosis clearly compounds the cardiotoxic effects of cocaine and may play a significant role in death from cocaine poisoning.

The patients described previously showed significant acidemia from severe cocaine toxicity. They had combined metabolic and respiratory acidoses attributable to seizures, agitation, and hypoventilation. Improved ventilation and sodium bicarbonate administration were followed quickly by normalization of the cardiac conduction pattern on correction of the blood pH. On presentation, all patients showed prolongation of the QRS complex and QTc interval. Variation was noted in the deviation of the overall and terminal 40 ms of the QRS axis. When the blood pH was increased to 7.40, there was a shortening of the QRS duration and QTc interval, and normalization of the QRS axes in all of the patients. The third patient, however, had essentially no change in the QTc interval and QRS axes. This may have been because of a lesser degree of toxicity (the other patients arrested and had lower pHs). Explanations of the mechanisms responsible for these changes and their

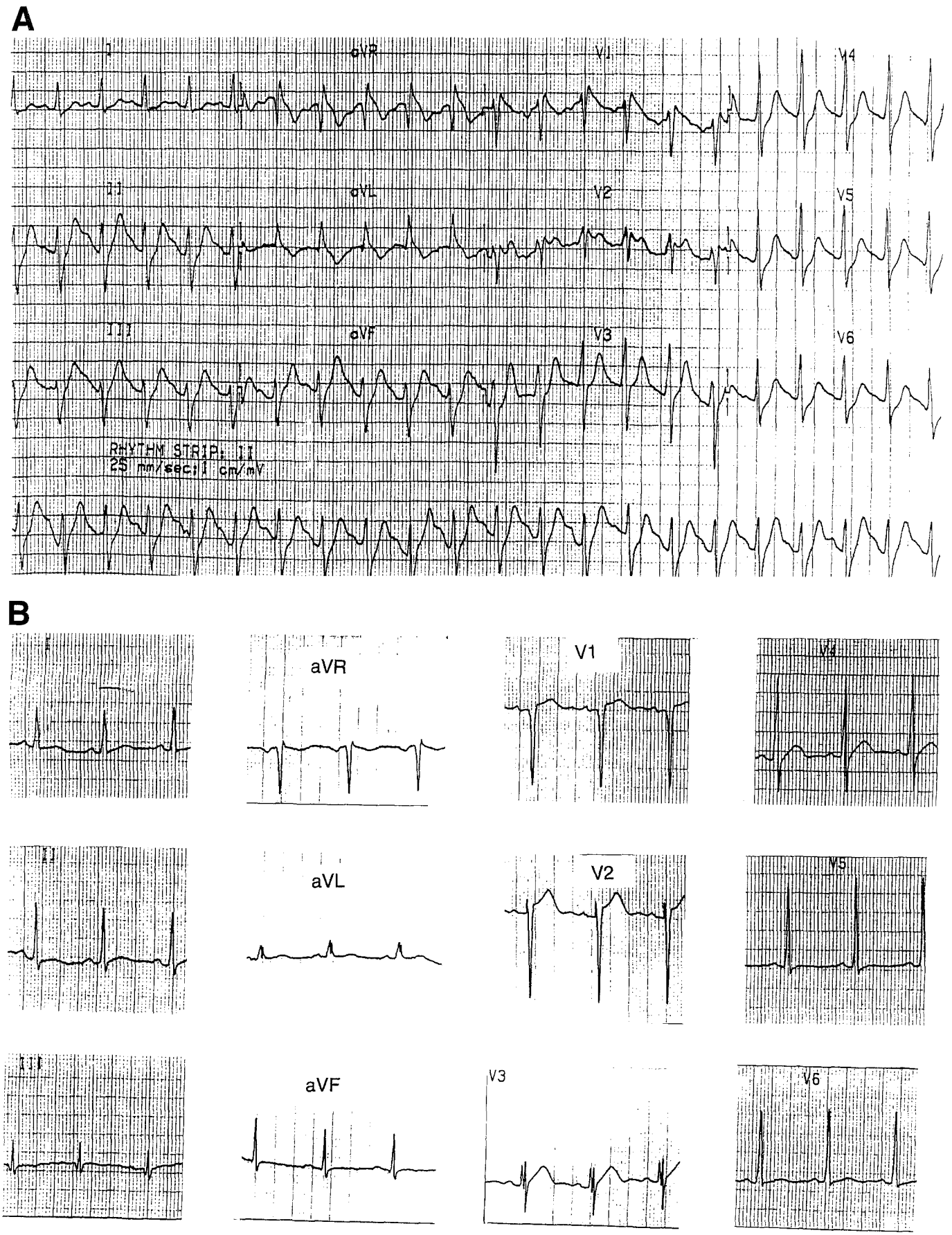

FIGURE 2. (A) Electrocardiogram of the patient in case 3 who presented with psychomotor agitation and hyperthermia after cocaine exposure. The arterial blood pH was 7.10. (B) Electrocardiogram of the patient in case 3 which was obtained 7 hours later. The patient was actively cooled and sedated. The arterial blood pH was 7.34.

TABLE 2. Admitting Arterial Blood Gas and Serum Potassium Results for the Patients

Patient	pH	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	Potassium (3.6-5.1 mEq/L*)
1	6.72	84	115	5.8
2	6.92	58	83	3.9
3	7.10	47	98	3.3
4	6.77	102	347	3.5

*Laboratory's normal reference range.

clinical significance (eg, axis deviations) are not known. However, changes in ionic concentrations are involved (as discussed earlier), and further investigations are necessary to better define their roles.

Two similar events of severe cocaine toxicity were described in the literature. One report involved a male cocaine body-packer who seized.[10] Hypotension and a wide complex idioventricular rhythm ensued. The initial blood pH was 6.83, and when it was corrected with ventilation and the administration of sodium bicarbonate, the blood pressure and rhythm normalized. The second report was a man who presented with status epilepticus, nonsustained periods of ventricular tachycardia and a blood pH of 6.55.[11] The patient was sedated, intubated, and administered sodium bicarbonate. The investigators reported resolution of the dysrhythmia with correction of the acidemia. Respiratory acidosis may be more significant than metabolic acidosis in contributing to cocaine cardiac toxicity because CO_2 readily crosses cell membranes to lower pH.[28] This would support the need for careful monitoring of the airway and ventilator status of these patients, and to provide support as necessary.

Control of seizures and psychomotor agitation is paramount in the management of patients with acute cocaine toxicity. When cocaine-induced seizures in dogs were prevented with the use of benzodiazepines, blood pH and body temperature remained normal and survival improved.[29] Benzodiazepines or barbiturates may be used for sedation, to blunt the sympathomimetic effects of cocaine on the heart, and to limit metabolic acidosis from muscle exertion. The presence of acidemia represents significant toxicity and must be treated immediately with either hyperventilation or the administration of sodium bicarbonate. Sodium bicarbonate may offer the additional benefit of counteracting the sodium channel blocking effect of cocaine on cardiac conduction and should be considered in the management of cocaine-induced wide complex tachycardia.[30] The benefits of bolus versus constant infusion administration of sodium bicarbonate in this setting remain to be determined. The short plasma half-life of cocaine and the acuteness of the precipitating event may favor intermittent therapy. Quinidine and procainamide are to be avoided in this setting because cardiac toxicity can be enhanced.[31] The use of catecholamines (eg, epinephrine) is cautioned because of the propensity for malignant dysrhythmias from increasing already elevated circulating catecholamine concentrations caused by cocaine and lactic acidemia.[5,15,32,33]

Other causes of cardiac conduction delays and seizures were evaluated, and not found in these patients. These included subarachnoid hemorrhage, electrolyte abnormalities, and toxins. Common agents responsible for prolongation of the QRS duration and QTc interval (eg, tricyclic antidepressants and phenothiazines) were not detected in the comprehensive drug screens. Although postresuscitative effects on the heart cannot be excluded as contributory findings on the ECG, this would only pertain to 2 of the 4 patients.[34] The clinical manifestations and course of these patients support their acute toxicity to cocaine and the importance of limiting factors that contribute to acidosis (eg, hyperthermia, seizures, psychomotor agitation). Good supportive care will correct acidemia and cardiac conduction disorders in patients with cocaine toxicity and promote a favorable outcome.

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