Cardiomyopathic Lentiginosis/LEOPARD Syndrome Presenting as Sudden Cardiac Arrest*

Alexander Woywodt, Julia Welzel, MD; Henning Haase, MD; Anke Duerholz, MD; Uwe Wiegand, MD; Juergen Potratz, MD; and Abdolhamid Sheikhzadeh, MD

A 26-year-old apparently healthy man with numerous pigmented skin lesions collapsed during an evening party and was resuscitated from ventricular fibrillation. Hypertrophic cardiomyopathy and subaortic tunnel were disclosed by angiocardioiography. A diagnosis of cardiomyopathic lentiginosis/lentigines (multiple), electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of the genitalia, retardation of growth, and deafness (sensorineural) syndrome was made. The patient then underwent treatment with an implantable pacemaker-defibrillator device. Further evaluation revealed several well-established features of the disorder. This is the first reported case of survival from ventricular fibrillation associated with this rare and little known multifaceted syndrome. Disseminated lentiginosis must prompt clinicians to evaluate such cases further since underlying disorders may be associated with considerable morbidity and, apparently, sudden death.

(CHEST 1998; 113:1415-17)

Key words: cardiac arrest; cardiomyopathic lentiginosis; hypertrophic nonobstructive cardiomyopathy; implantable pacemaker-defibrillator; lentigines; LEOPARD syndrome; subaortic tunnel

Hypertrophic cardiomyopathy occasionally is associated not only with sudden death and different congenital malformations, such as Noonan’s syndrome, hereditary spinal (Friedreich’s) ataxia, and dwarfism with cryptorchism,1 but also with abnormalities of cutaneous pigmentation (cardiomyopathic lentiginosis2 or lentigines [multiple], electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of the genitalia, retardation of growth, and deafness [sensorineural] syndrome [LEOPARD syndrome]).3-5

The case reported here is that of a young man with apical nonobstructive cardiomyopathy associated with lentiginosis and a variety of clinical disorders who was successfully resuscitated from ventricular fibrillation.

Case Report

An apparently healthy 26-year-old man was admitted to the ICU after successful resuscitation from documented ventricular fibrillation sustained during dancing the polka. A comprehensive past medical history could be obtained from his mother: “moles” had erupted during childhood; a dermatologist had diagnosed nevi and had recommended surveillance. In 1980, an operation was performed for an undescended testicle; an aneurysm of the left femoral vein was excised in 1988. In 1991, ultrasound studies disclosed splenomegaly and a dystopic right kidney. He had repeatedly noted pitting edema and lost consciousness during exercise. The patient worked as a shop assistant; he had no children. His ancestors were of German and Eastern European origin; abnormal pigmentation, heart disease, syncope, and sudden death had not been reported among his family.

On examination, he was 1.92 m tall and weighed 56 kg. Hypertelorism, brevicolli, and pterygium colli were noted. Myriads of pinpoint to lentil-sized dark-brown macular lesions were present on the arms, legs, and back, whereas the abdomen and face were markedly spared (Fig 1).

The patient was found to have pectus excavatum and the apical beat was thrusting; first and second heart sounds were normal; a loud systolic murmur with midystolic click was audible over the apex. Scoliosis, cubitus valgus, and brachydactyly were evident. An ECG showed first-grade atrioventricular block, incomplete right bundle block with an RsR pattern, giant negative T waves in V3-V6, and left posterior hemiblock. QT, QTc, JT, and JTc intervals, respectively, were within normal limits. A chest radiograph showed enlargement of the left atrium and ventricle with a cardiothoracic ratio of 20:33. Echocardiography demonstrated hypertrophy of the interventricular septum to an end-systolic width of 16 mm and mitral valve prolapse with minimal regurgitation. Invasive studies ruled out coronary heart disease but left ventricular angiocardioiography showed systolic mouse-tail phenomenon consistent with apical hypertrophic nonobstructive cardiomyopathy. The aortic cusp of the mitral valve was grossly enlarged and prolapsed with minimal mitral regurgitation. A long, goose-neck-like subaortic muscular tunnel without stenosis was present (Fig 2). The right atrium and ventricle were normal. There was no shunt, and hemodynamic parameters were within normal limits. Electrophysiologic testing disclosed no abnormalities. Punch biopsy of a skin lesion confirmed lentigo simplex. A CT scan revealed reduction in brain volume and a left frontal arachnoidal cyst with concomitant reduction in bone thickness. Audiometry disclosed mild unilateral sensorineural hearing loss. The patient made an uneventful recovery, a pacemaker-defibrillator device (Jewel 7221; Medtronic; Duesseldorf, Germany) was implanted, and he was discharged on metoprolol without sequelae of the incident.

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Sudden ventricular fibrillation is uncommon in young adults. Unlike in the elderly, coronary heart disease is rarely the cause. Instead, myocarditis, cardiomyopathy, right ventricular dysplasia, use of illicit drugs, and anomalies of the QT interval prevail. Hypertrophic cardiomyopathy is a key feature of cardiomyopathic lentiginosis. Interestingly, sudden death has been mentioned in previous reports of the disorder.

In this case, cardiomyopathy was revealed as the most
likely cause and concomitant lentiginosis prompted evaluation for a unifying diagnosis. Disorders of pigmentation have been reported in association with various cardiac abnormalities, but classification remains controversial. Features of both cardiomyopathic lentiginosis and LEOPARD syndrome, a mnemonic code for lentiginosis, ECG changes, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, growth retardation, and deafness, were present. Pectus excavatum, skull defects, and other skeletal abnormalities as well as anomalies of the genitalia, such as undescended testicle, are frequently encountered whereas involvement of the urinary tract is believed to be rare. Somatic retardation is common. The presence of brain atrophy may indicate that mental impairment, one of the syndrome’s key features, might ensue in the future. Finally, additional cases among the kindred of this patient were not detected; this suggests that a novel mutation may have occurred.

Both LEOPARD syndrome and cardiomyopathic lentiginosis, originally proposed to be distinct entities, have salient features in common, not the least of which is their mode of inheritance as an autosomal dominant trait and their preponderance to affect tissues of neural crest origin. It, therefore, seems intriguing to assume that both reflect variable penetrance and expression of the same genetic defect. Among other features, atrial myxoma, mitral regurgitation, and, recently, recurrent arterial dissection have been reported in lentiginosis and may be variant forms of the disorder. The genetic basis of lentiginosis syndromes, however, remains entirely unknown, thus preventing proper classification and diagnosis.

**CONCLUSION**

Lentiginosis must prompt thorough evaluation since it may be part of a multifaceted syndrome that cannot only be associated with considerable morbidity but may even place patients at risk for sudden death. Although identification of patients in need of prophylactic treatment will remain difficult, pacer-cardioverter-defibrillator device therapy is believed to be indicated and beneficial in survivors of out-of-hospital ventricular fibrillation.

**REFERENCES**


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**Coronary Artery Spasm Complicating Anaphylaxis Secondary To Skin Disinfectant**

Viviane M. A. Conraads, MD; Philippe G. Jorens, MD; Didier G. Ebo, MD; Marc J. Claey, MD; Johan M. Bosmans, MD; and Christiaan J. Vrints, MD

We report a patient in whom presumed vasospasm of an angiographically normal coronary artery led to severe transmural myocardial ischemia. To our knowledge, this is the first case in which an allergic reaction to locally applied chlorhexidine caused such a severe reaction. *(CHEST 1998; 113:1417-19)*

**Key words:** anaphylaxis; chlorhexidine; coronary; vasospasm

A patient sustained two anaphylactic reactions accompanied by severe myocardial ischemia caused by presumed coronary artery vasospasm. Immunologic testing indicated chlorhexidine as the culprit substance. This case emphasizes the fact that severe anaphylaxis can result in dramatic cardiac changes secondary to the systemic and local release of vasoconstrictive mediators. It should be stressed, however, that subclinical coronary atherosclerosis can be unmasked, merely by the fact of severe vasodilative shock.

**CASE REPORT**

A 53-year-old man with no history of cardiac disease was referred for curative resection of the upper lobe of the left lung because of adenocarcinoma. Ten minutes before anesthetic induction, a test dose of cefazolin was administered. The patient subsequently received propofol, sufentanil, and atracurium. Fifteen minutes later, profound hypotension developed (BP, 45/30 mm Hg; pulse rate, 130/min) and the monitor showed diffuse ST depression. The patient was resuscitated with ephedrine, 40 mg; epinephrine, 0.2 mg/kg/min; and promethazine 50 mg, ST segment normalized rapidly (Fig 1, A). After IV administration of 1 g of tranexamic acid, infusion of nitroglycerin 2.5 μg/kg/min, and promethazine 50 mg, ST segments normalized rapidly (Fig 1, B). Serially determined cardiac enzymes were elevated.

**DISCUSSION**

We report here the first case of coronary artery spasm to result from an allergic reaction to chlorhexidine. This patient was sensitized to chlorhexidine and subsequently reacted after subcutaneous administration of chlorhexidine. The sensitivity test result was positive (Fig 2).

**CONCLUSION**

Anaphylaxis can be associated with coronary artery spasm. Further clinical studies are needed to define the epidemiology of this local reaction to skin disinfectant.
enzyme levels excluded myocardial necrosis. Findings from coronary arteriography were completely normal. After two episodes of life-threatening shock and only several days after major surgery, it was considered medically inappropriate to proceed to pharmacologic testing for coronary spasm.

An extensive immunologic investigation was performed; tests included serum-specific IgE measurement and immediate skin testing for various antibiotics, analgesics, muscle relaxants, and disinfectants. Whereas healthy volunteers failed to react to the substance, a prick test with 2% chlorhexidine digluconate in 70% alcohol was strongly positive in the patient, clearly suggesting that Hibitane was the culprit.

**DISCUSSION**

Severe anaphylaxis may induce bronchospasm, profound vasodilation, and angioedema. In such cases, underlying subclinical coronary atherosclerosis can become clinically evident. Anaphylaxis may induce an acute ischemic burden due to the combination of reduced coronary perfusion pressure, tachycardia, and sometimes severe hypoxia. This combination of events may hamper an adequate cardiac response to the extreme vasodilation and even lead to a reduced cardiac output and further deterioration.

The therapeutic administration of α-agonists (e.g., epinephrine, ephedrine) will induce an inotropic and chronotropic response that leads to peripheral and possibly coronary vasoconstriction. An acute rise in shear stress can elicit disruption of an unstable coronary plaque, resulting in platelet aggregation and the release of potent vasoconstrictors (thromboxane and serotonin). This creates the ideal environment for coronary occlusion. Moreover, Kovanen et al demonstrated the presence of activated mast cells at the site of ruptured coronary artery plaques, raising the question of whether an allergic reaction, by triggering the release of mast cell contents, could promote plaque disruption.

Since no underlying coronary artery disease was detected in our patient, the theory of a pure coronary spasm is preferred. Coronary vasoconstriction is a well-established feature of anaphylaxis, which is characterized by a massive systemic release of several mediators. These substances include histamine, catecholamines, serotonin, leukotrienes, and prostaglandins, which are all capable of modifying coronary tone and significantly influencing platelet aggregation and thrombosis. Perivascular and cardiac mast cells have been implicated in the pathogenesis of coronary artery spasm. The effects of histamine on cardiac function (chronotropism, dromotropism, inotrop-
pism, bathmotropism) are mediated via H₁ and H₂ receptors. Vigorito et al. showed, in a human model, that the IV administration of histamine could elicit two different reactions. In a subgroup of patients with atypical angina or valvular heart disease and normal coronary arteries, the stimulation of H₁ receptors induced vasodilation of small coronary resistance vessels. However, in a substantial proportion of patients with vasospastic angina independent of coronary artery disease, histamine provoked vasoconstriction of large capacitance coronary arteries. This finding supports the role of the systemic and local release of histamine during anaphylaxis complicated by coronary vasospasm. Ginsburg et al. in a model of isolated human epicardial coronary arteries, showed that histamine has a very potent vasoconstrictive effect, probably mediated via H₁ receptors, whereas H₂ receptor stimulation induces vasodilation. The vasoconstrictive effect of histamine in patients with vasospastic angina and morphologically normal coronary arteries is most probably the result of a defective endothelial nitric oxide-mediated vasodilation due to subclinical early coronary atherosclerosis. Although coronary vasospasm has been reported during allergic reactions against wasp stings, antibiotics, nonsteroidal anti-inflammatory drugs, glafenine, and contrast agents, to our knowledge this is the first reported case initiated by a locally administered substance.

In conclusion, anaphylactic reactions can cause such major hemodynamic changes that unmask previously unknown coronary disease. In such situations, fast recovery from the extreme peripheral vasodilation and tachycardia is crucial. On the other hand, the massive release of potent coronary vasoconstrictive mediators may lead to coronary vasospasm, mimicking acute myocardial infarction. Coronary angiography may be needed to define coronary anatomy. Immunologic identification of the causative factor is crucial in order to prevent similar catastrophes in an anaphylactic patient.

REFERENCES

False Elevation of Serum Creatinine Following Skin Absorption of Nitromethane Complicates the Clinical Diagnosis of Rhabdomyolysis*

Andrea Gabrielli, MD; and Catherine Hamnett-Stabler, PhD

A patient had extensive blunt trauma from a high-speed crash in which nitromethane fuel erupted from the fuel tank and soaked into his protective multilayer jumpsuit. The clinical diagnosis was complicated because the absorption of nitromethane fuel through the skin and by inhalation falsely increased the serum creatinine value when a modified Jaffe reaction was used in the laboratory. This spurious value was “unmasked” by the use of an enzymatic method to measure the serum creatinine level. A high serum creatinine value disproportionate to the level of BUN and recent skin exposure to nitromethane were the clinical indications that suggested the differentiation of massive rhabdomyolysis from spurious hypercreatinemia. This spurious value was a confounding factor in the diagnosis of crush syndrome and rhabdomyolysis.

(CHEST 1998; 113:1419-22)

Key words: absorption; nitromethane; rhabdomyolysis; skin

Rhabdomyolysis results when skeletal muscle is injured and toxic intracellular components are released into the systemic circulation. Biochemical hallmarks of this syndrome include increased serum creatine kinase level.

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nyogrobilinemia, and myoglobininuria. This case report describes a patient whose clinical picture suggested a diagnosis of rhabdomyolysis secondary to blunt trauma of the chest and extremities; however, a high serum creatinine concentration and normal BUN concentration at admission complicated the clinical diagnosis.

**CASE REPORT**

A 25-year-old man was involved in a crash, at an estimated speed of 290 miles per hour, while professionally racing a dragster. Emergency personnel at the race track noted that the patient was awake and that his protective, multilayered jumpsuit was partially burned, and that the jumpsuit and underwear were soaked with fuel from the car’s fuel tank. The jumpsuit was removed, the patient was stabilized, and then he was transferred by air ambulance to the local hospital. On admission to the emergency department, his Glasgow coma score was 15 and he had retrograde amnesia as a result of the accident. His blood pressure was 107/52 mm Hg, heart rate was 92 beats/min, and respiratory rate was 25 to 30 breaths/min. Multiple bruises and lacerations were present; there was no sign of burn injury to his skin.

The patient was in moderate respiratory distress with an oxygen saturation level between 90 and 95% while breathing 100% oxygen through a nonbreathing face mask. A moderate amount of hemoptysis was noted. The patient was electively intubated for airway protection, and a fiberoptic tracheobronchoscopy was performed to assess the integrity of the tracheobronchial tree. A CT scan of the head was normal. Radiographic studies showed a C-7 spinous process fracture, patellar avulsion without fracture, and evidence of right and left pulmonary contusions with a small pneumomediastinum and subcutaneous emphysema, without evidence of pneumothorax. Because the patient’s injuries resulted from a high-speed crash, and a pneumomediastinum had receded spontaneously. The patient was extubated and transferred to the ward. The patient’s serum creatinine concentration was followed up daily and decreased from a peak of 17.5 to 0.8 mg/dL in 13 days (Table 1). Myoglobin was still not found in the urine. An echocardiogram 1 day after admission showed no signs of myocardial contusion. Four days after admission, the patient’s general condition and chest contusion had improved, and the pneumomediastinum had receded spontaneously. The patient was extubated and transferred to the ward.

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### Table 1—Laboratory Test Results for Patient

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Normal Range</th>
<th>Admission</th>
<th>3-h PA*</th>
<th>5-h PA*</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
<th>Day 11</th>
<th>Day 12</th>
<th>Day 13</th>
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<tr>
<td>Creatinine</td>
<td>0.5-1.2 mg/dL</td>
<td>8.6</td>
<td>17.5</td>
<td>14.2</td>
<td>13.9</td>
<td>8.6</td>
<td>5.1</td>
<td>3.1</td>
<td>1.9</td>
<td>1.3</td>
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<tr>
<td>BUN</td>
<td>10-20 mg/dL</td>
<td>12</td>
<td>13</td>
<td>11</td>
<td>11</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>7</td>
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<td>13</td>
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<tr>
<td>Creatine kinase</td>
<td>5-150 U/L</td>
<td>—</td>
<td>—</td>
<td>1,268</td>
<td>1,852</td>
<td>3,160</td>
<td>2,664</td>
<td>3,180</td>
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<tr>
<td>Creatine kinase MB</td>
<td>0.2-9 mg/L</td>
<td>—</td>
<td>—</td>
<td>26.7</td>
<td>36.5</td>
<td>2.3</td>
<td>6.2</td>
<td>5.3</td>
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<td>Sodium</td>
<td>135-145 mEq/L</td>
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<td>141</td>
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<tr>
<td>Potassium</td>
<td>3.5-5.0 mEq/L</td>
<td>3.2</td>
<td>4</td>
<td>4.3</td>
<td>3.8</td>
<td>3.5</td>
<td>3.9</td>
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<td>Chloride</td>
<td>95-105 mEq/L</td>
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<td>109</td>
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<td>CO₂</td>
<td>24-32 mEq/L</td>
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<td>17</td>
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<td>Serum osmolality</td>
<td>275-295 mOsm/kg</td>
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<td>—</td>
<td>289</td>
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<td>Urine osmolality</td>
<td>50-1,100 mOsm/kg</td>
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<td>Urinalysis</td>
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*PA=postadmission.*
increased sarcolemmal sodium and calcium influx, intracellular acidosis, adenosine triphosphate depletion, and cell death. Restoration of blood flow, when feasible, allows the movement of neutrophils into the necrotic area and the release of free radicals in the cell microenvironment. Cell death is enhanced through a mechanism of reperfusion injury.  

The concentration of creatinine in muscle is approximately 4 mg/100 g of tissue. 8 The patient in this report weighed 80 kg. Calculating the extracellular space as 60% of total body weight, damage to 1 kg of muscle would have increased the serum creatinine concentration to 0.12 mg/dL. It is impossible to evaluate the exact amount of muscle damage. However, even if one assumes that 10% of the body muscular mass was damaged and its content released completely in 24 h into the extracellular space, the creatinine should not have increased by more than 1.2 mg/dL.

Another mechanism that could explain the increase of serum creatinine is the conversion of intracellular creatine and creatine phosphate to creatinine. This conversion rate is <3%/d in patients with a normal pH level and a temperature of 38°C, 9 and would have been responsible for only a negligible increase in this patient.

A high creatinine-to-BUN ratio was described in 903 crush-injury patients with acute renal failure. 9 These patients had an average creatinine-to-BUN ratio of 0.0187 within 24 h of the injury. Their median creatine kinase activity was 21,775 U/L, 13 times higher than the initial creatine kinase activity in our patient. These patients were predominantly young men, as was the reported patient, who because of greater muscle mass than average have increased sarcolemmal sodium and calcium influx, intra- cellular acidosis, adenosine triphosphate depletion, and cell death. Restoration of blood flow, when feasible, allows the movement of neutrophils into the necrotic area and the release of free radicals in the cell microenvironment. Cell death is enhanced through a mechanism of reperfusion injury.  

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Other biochemical features associated with severe crush injury syndromes are hyperkalemia and often severe hypercalcemia. Neither of these conditions was present in the reported patient.

What made the reported patient's clinical presentation unique was the high creatinine level on admission; this level peaked in a manner similar to that observed in patients with untreated chronic renal failure. Thus, despite the circumstances of the accident, the initial clinical presentation, the BUN, and the creatine kinase activities did not correlate with the very high creatinine level. In particular, the maximum creatine kinase activity observed at 3,180 U/L within 5 days suggests clinically mild rhabdomyolysis; this was confirmed by the lack of myoglobin in the urine. Additionally, none of the other metabolic markers were suggestive of renal function impairment. For example, despite the calculated low creatinine clearance of 5.5 mL/min, the urine osmolarity was “appropriately” concentrated at 826 mOsm/kg, and the urine output was optimal. After repeated measurement of creatinine confirmed the early high concentration, the presence of an interfering substance was suspected.

The Jaffe reaction that was used to measure creatinine is nonspecific and other chemicals besides creatinine can react with the picric acid, thus leading to an apparent increase in the creatinine concentration. A number of modifications to the assay are in use today to lessen this problem. Chemicals known to cause this type of interference include glucose, acetone and ketoacids, ascorbic acid, as well as some of the cephalosporins. Most of these interfere when present in high concentrations. This patient was not receiving any of the drugs known to cause this increase, and his glucose level was not sufficiently elevated to cause such an increase. Therefore, one may suppose that interference by these chemicals was not a factor in this case. A review of the fuel mixture that had saturated this patient's clothing at the accident scene showed the fuel to be 95 to 98% nitromethane with 2 to 5% methanol. Short-distance racing cars and model engines use this type of fuel. This patient, it may be suspected, had absorbed a substantial amount of nitromethane both through the skin and by inhalation.

Nitromethane is used as a stabilizer for chlorinated hydrocarbons, as a compound of special fuels for internal combustion engines, and as a solvent.11 A colorless and odorless fluid, nitromethane is flammable, and when ignited, it burns with an almost invisible, colorless flame that often self-extinguishes or can be easily extinguished by water. Resins with extensive commercial applications, such as vinyl, epoxy, and polyanide and acrylic polymers, are soluble in nitroparaffins, such as nitromethane.

Nitromethane can explode if subjected to a severe shock while under confinement in heavy-walled pressurized containers. Heating a solution of nitromethane to approximately 350°C also may result in an explosion. The combination of high pressure and temperature is used as an energy source for short-distance, high-speed vehicle engines, such as those in top-fuel race cars.

The toxicology of nitromethane has been extensively studied in animal models. The most common lesions described after acute intoxication are tubular cell edema in the kidney and liver and spleen hemorrhagic congestion.12,13 A massive acute overdose of nitromethane in animals results in death and is preceded by acute excitations of the convulsive type.13 A study of skin and mucosal toxicity with chronic exposure to nitromethane in animal models showed only dry skin because of the defatting action of the compound.14 The American Conference of Governmental Industrial Hygienists has established 100 ppm as the threshold limit for nitromethane vapor exposure per 8 h.14

Only one case of nitromethane toxicity has been reported previously. In this case the patient ingested model airplane fuel in a suicide attempt.15 The concentration of nitromethane in this type of fuel is only 10 to 30%. A high serum creatinine level (8.0 mmol/L), which was measured using a modified Jaffe reaction, was reported in this case. A modified Jaffe reaction also is used in the laboratory for measuring the values for the patient reported in this study. As with many of the chemicals known to interfere with methods using this reaction, nitromethane contains a reactive methyl group, which reacts with the picric acid used in the assay. As in the previously reported case, when samples from the reported patient were tested using a
more specific enzymatic method, normal creatinine concentration was found. As far as can be determined, this is the first time that such an interference with the analytical method can be attributed to skin absorption and inhalation of nitromethane. In the case reported here, the history of severe blunt trauma associated with elevated creatine kinase activity complicated the clinical diagnosis.

Nitromethane is considered by most industrial toxicologists as only slightly toxic when ingested and even less toxic when inhaled or absorbed via the skin. This case report demonstrates that skin absorption of nitromethane can interfere with the measurement of serum creatinine when a modified Jaffe reaction is used. This interference may complicate the clinical picture. As far as can be determined, this is the first case that describes such interference in a patient who had absorbed nitromethane through the skin.

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