

Mechanism of Cocaine-Induced Hyperthermia in Humans

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Background: The lethal effects of cocaine are unique among those of other illicit drugs because cocaine has the propensity to cause hyperthermia. The traditional view is that cocaine causes a hypermetabolic state with increased heat production. However, because cocaine-induced hyperthermia occurs primarily in hot weather, it is hypothesized that cocaine also impairs thermoregulatory adjustments that mediate heat dissipation.

Objective: To test the effects of cocaine on body temperature regulation in humans.

Design: Randomized, double-blind, placebo-controlled crossover trial.

Setting: A cardiovascular physiology laboratory in Dallas, Texas.

Participants: 7 healthy, cocaine-naive volunteers.

Intervention: Progressive passive heat stress, during which each participant received intranasal cocaine (2 mg/kg of body weight) or placebo (lidocaine, 2 mg/kg).

Measurements: Esophageal temperature, skin blood flow, sweat rate, and perceived thermal sensation.

Results: Three major new findings were noted. First, cocaine substantially augmented the progressive increase in esophageal temperature during heat stress ($P < 0.001$). Second, this augmentation was explained by a rightward shift in the esophageal temperature threshold for the onset of both cutaneous vasodilation (37.37 ± 0.09 °C for cocaine vs. 37.06 ± 0.07 °C for lidocaine; $P = 0.01$) and sweating (37.38 ± 0.09 °C for cocaine vs. 37.07 ± 0.06 °C for lidocaine; $P = 0.002$). Third, cocaine paradoxically impaired the perception of heating by attenuating the progressive increase in thermal discomfort associated with heat stress.

Conclusions: In humans, impaired heat dissipation is a major mechanism by which cocaine elevates body temperature. When healthy, cocaine-naive persons are subjected to passive heating, pretreatment with even a small dose of intranasal cocaine impairs sweating and cutaneous vasodilation (the major autonomic adjustments to thermal stress) and heat perception (the key trigger for behavioral adjustments).

Ann Intern Med. 2002;136:785-791.

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Cocaine abuse is a major cause of life-threatening cardiovascular emergencies, including hypertensive crisis, acute myocardial infarction, and ventricular arrhythmias. The lethal effect of cocaine is unique among those of other illicit drugs because it is related not only to dose but also to cocaine's propensity to cause hyperthermia. Although fatal cocaine overdose typically is associated with high blood cocaine levels (3 to 6 mg/L) (1), cocaine-related deaths can also occur when hyperthermia is present at blood levels 10 to 20 times lower (2). The intrinsic thermogenic property of cocaine underlies recent epidemiologic data indicating that mortality rates for cocaine overdose increase substantially in hot weather (3). This temperature-dependent increase in mortality rates is specific to cocaine and is not seen with opiates or other illicit drugs. These clinical observations are bolstered by experiments in dogs demonstrating that cocaine-induced death can be eliminated by multiple strategies that prevent hyperthermia (4). In humans, however, the underlying mechanisms mediating cocaine-induced hyperthermia are poorly understood.

The hyperthermic properties of cocaine have been

attributed largely to a hypermetabolic state (agitation with increased locomotor activity) that increases heat production (5). Indeed, cocaine-induced hyperthermia has been likened to two other syndromes, neuroleptic malignant syndrome and malignant hyperthermia, that are characterized by hyperpyrexia, delirium, tachycardia, and elevated blood pressure (6, 7). In both of those syndromes, excessive heat production due to involuntary muscle contraction is sufficient to raise body temperature even in a cool environment (for example, an operating room). In contrast, cocaine-induced hyperthermia is seen primarily in the setting of high ambient temperatures. We therefore hypothesized that, in addition to increased heat production, impaired heat dissipation is another important mechanism contributing to the hyperthermic properties of cocaine.

When body temperature increases above thermoregulatory set points, heat dissipation depends on both autonomic and behavioral adjustments. The major autonomic adjustments include activation of sympathetic cholinergic fibers that leads to sweating and cutaneous vasodilation (8). The behavioral adjustments are

Context

The cause of hyperthermia in cocaine abuse is not well understood. Both excess heat generation and defective heat dissipation are potential causes of fatal hyperthermia.

Contribution

Nasal administration of cocaine causes greater increase in core body temperature, decrease in heat perception, and greater impairment of sweating and skin blood flow compared with nasal lidocaine administration.

Implications

Excessive heat production, impaired heat dissipation, and alteration of behavioral responses to increased body temperature may lead to fatal hyperthermia in cocaine abusers.

—The Editors

prompted by thermal discomfort and include heat avoidance and external cooling. In humans, these simple behavioral responses can be more important than autonomic adjustments in maintaining normal body temperature during heat stress (9).

We sought to test the effect of cocaine on thermoregulatory adjustments in humans. Because cocaine has a profound influence on both cardiovascular and cognitive function, we conducted a randomized, placebo-controlled study to assess the effects of a low, noneuphoric dose of intranasal cocaine on autonomic and behavioral thermoregulation in healthy cocaine-naive volunteers.

METHODS**Participants**

We studied 7 healthy male and female volunteers who ranged in age from 23 to 37 years. The Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas, Texas, approved the protocol, and all volunteers provided written informed consent. All participants were normotensive and had no history of cardiovascular disease, cocaine abuse, or other recreational drug use. No participant was taking prescription or nonprescription drugs with cardiovascular or autonomic effects. Participants refrained from smoking cigarettes or drinking alcohol- or caffeine-containing beverages for at least 12 hours before the experiment.

Measurements

Internal temperature was measured by using a thermistor placed in the esophagus at a depth equal to 25% of each participant's standing height, and skin temperature was measured from the weighted electrical average of six thermocouples attached to the skin. Each participant wore a tube-lined suit that controlled skin temperature by changing the temperature of the water perfusing the suit. The suit covered the entire body surface with the exception of the head, arms, and feet. We assessed skin blood flow from each participant's forearm during heat stress. The water-perfused suit did not cover the forearm where skin blood flow measurements were obtained; thus, any change in skin blood flow during heat stress was not directly related to mechanisms associated with local heating. Skin blood flow was measured by using multifiber laser Doppler flowmeter (Perimed, North Royalton, Ohio). Heart rate was obtained from the electrocardiogram by using a cardiometer (CWE, Inc., Ardmore, Pennsylvania), and blood pressure was obtained by using the oscillometric technique (Welch Allyn, Beaverton, Oregon). Mean arterial blood pressure was calculated as one third of the pulse pressure plus diastolic blood pressure. Cutaneous vascular conductance, which is the reciprocal of vascular resistance, was calculated from the ratio of the laser Doppler signal to mean arterial pressure.

Forearm sweat rate was measured continuously with the ventilated capsule method, in which a capsule with a window of 2.8 cm² is attached to the surface of the skin. Nitrogen gas is perfused through the capsule at a fixed rate, and as the person begins to sweat, the water on the skin evaporates through the window into the nitrogen gas. The humidity of the effluent nitrogen gas is quantified through a humidity detector "downstream" from the capsule. The sweat rate is then calculated from the humidity, temperature, and flow of the nitrogen gas. Throughout the heat stress, participants rated thermal sensation by using a standardized 9-point thermal comfort scale ranging from 4.0 (neutral) to 8.0 (unbearably hot) at increments of 0.5 (10).

Experimental Protocol

All experiments were conducted with the participants in a supine position. In a randomized, double-blind, crossover trial, each participant was exposed to

whole-body heating after receiving intranasal cocaine hydrochloride (2 mg/kg of body weight, 10% solution) or lidocaine hydrochloride (2 mg/kg, 10% solution). Lidocaine was used as an internal control for the local anesthetic property of cocaine (11). The experiments were conducted on 2 separate days, at the same time of day, 3 to 6 days apart. The dose of cocaine administered is half the standard dose administered for rhinolaryngologic procedures (12). The heat stress test was performed by perfusing the tube-lined suit with water at 46 °C. To assess maximal vasodilator responses, a heater surrounding the laser Doppler flow probe was used on completion of the heat stress to increase local skin temperature to 42 °C for 30 minutes. Heating the skin at this temperature and duration elicits maximal cutaneous vasodilation (13). Skin blood flow during the final minutes of this 30-minute procedure was averaged, and maximal cutaneous vascular conductance was then calculated from the ratio of that value and mean arterial blood pressure. Values for cutaneous vascular conductance were then normalized to percentages of maximum for that site (13).

Data Collection

Temperatures, skin blood flow, and sweat rate data were sampled at 50 Hz (Biopac, Santa Barbara, California). The electrocardiogram was sampled by a cardiota-chometer at 1000 Hz, using a multichannel digital data recorder (CWE, Inc.). These values were reduced to 20-second averages before statistical analysis. When cutaneous vascular conductance and sweat rate are plotted relative to esophageal temperature, two important variables can be identified to assess thermoregulatory function (14): the esophageal temperature threshold at which cutaneous vasodilation and sweating begin, and the slope of the line relating progressive elevations in cutaneous vascular conductance and sweating to increasing esophageal temperature. Esophageal temperature thresholds at which cutaneous vascular conductance and sweat rate began to increase were identified from individual plots of esophageal temperature versus cutaneous vascular conductance and esophageal temperature versus sweat rate. These points were selected as the internal temperatures at which pronounced and sustained increases in cutaneous vascular conductance and sweating were evident during the heating procedure. The investigator identifying these thresholds was blinded to the

participants and to their experimental conditions (lidocaine or cocaine).

Statistical Analysis

Statistical comparisons of temperature thresholds and slopes during cocaine and lidocaine administration were performed by using the paired *t*-test. Differences in responses (internal temperature, skin temperature, cutaneous vascular conductance, and sweat rate) during cocaine and lidocaine administration throughout the heat stress were statistically analyzed by using two-way repeated-measures analysis of variance (SigmaStat 2.0, SPSS Science, Chicago, Illinois). Treatment order was also assessed in the models, and no effect of treatment order on any outcome variables was found. The effects of cocaine on thermal sensation were statistically analyzed by comparing the internal temperature at each perceived heating score between 5.0 and 7.5 using paired *t*-tests. All values are reported as the mean (\pm SE), and the α level for all statistical analyses was set at 0.05.

Role of the Funding Sources

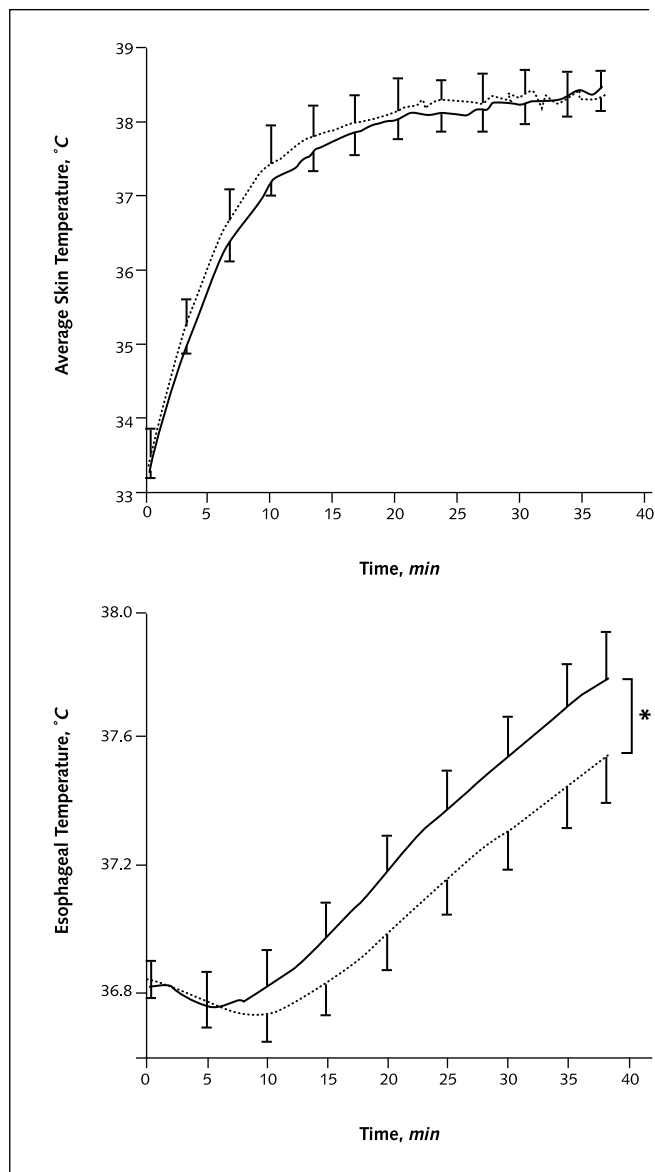
The funding sources had no role in the design, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Before heat stress, cocaine had no effect on esophageal temperature compared with lidocaine (36.79 ± 0.01 °C vs. 36.75 ± 0.08 °C). However, cocaine significantly increased mean arterial pressure (93 ± 3 mm Hg vs. 85 ± 3 mm Hg; $P = 0.001$) and heart rate (74 ± 5 beats/min vs. 67 ± 4 beats/min; $P = 0.01$). Cocaine had no significant effect on cutaneous vascular conductance before heat stress ($9 \pm 2\%$ of maximum vs. $7 \pm 2\%$ of maximum; $P = 0.09$).

Heat stress had no effect on mean arterial pressure during cocaine or lidocaine administration (93 ± 3 to 92 ± 2 mm Hg and 85 ± 3 to 87 ± 2 mm Hg, respectively) but significantly increased heart rate for both conditions (74 ± 5 to 107 ± 5 beats/min and 67 ± 4 to 105 ± 5 beats/min, respectively). However, mean arterial pressure at the end of heat stress was still significantly higher during cocaine administration than during lidocaine administration (92 ± 2 mm Hg vs. 87 ± 2 mm Hg, respectively; $P < 0.01$), whereas heart rate did not differ significantly between agents (107 ± 5 beats/

Figure 1. Responses of average skin temperature and esophageal temperature to cocaine (solid lines) and lidocaine (dotted lines) during whole-body heating.



Data are the mean (\pm SE). * $P < 0.001$ for cocaine vs. lidocaine.

min vs. 105 ± 5 beats/min; $P > 0.2$). Passive heating yielded comparable increases in skin temperature during both cocaine and lidocaine administration, confirming that the external heat stress applied was identical on both days (Figure 1, top).

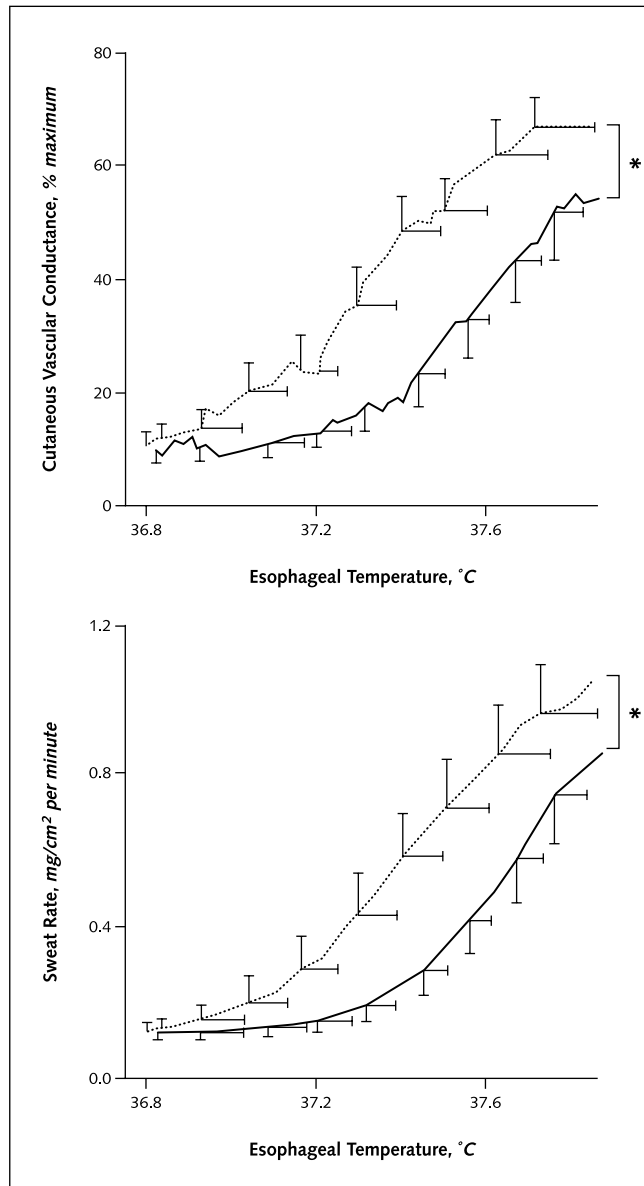
These results represent three major new findings. First, compared with lidocaine, cocaine significantly

augmented the progressive increase in esophageal temperature during heat stress ($P < 0.001$) (Figure 1, bottom). Second, cocaine also significantly attenuated the progressive increase in cutaneous vascular conductance and sweating during heat stress (Figure 2). At the highest common esophageal temperature of 37.86°C , cutaneous vascular conductance ($49 \pm 9\%$ of maximum vs. $70 \pm 5\%$ of maximum; $P = 0.03$) and sweat rate (0.8 ± 0.2 mg/cm² per minute vs. 1.0 ± 0.1 mg/cm² per minute; $P = 0.04$) were significantly lower during cocaine administration than during lidocaine administration (Figure 2). The cocaine-induced decrease in cutaneous vasodilation and sweating during heat stress was related to a delay in the onset of these thermoregulatory responses. This is evident by significant increases in the esophageal temperature thresholds for cutaneous vasodilation ($37.37 \pm 0.09^\circ\text{C}$ for cocaine vs. $37.06 \pm 0.07^\circ\text{C}$ for lidocaine; $P = 0.01$) and sweating ($37.38 \pm 0.09^\circ\text{C}$ for cocaine vs. $37.07 \pm 0.06^\circ\text{C}$ for lidocaine; $P = 0.002$), with no change in the slopes of these relationships. Third, although cocaine augmented the progressive increase in esophageal temperature during heat stress, it paradoxically attenuated the increase in thermal discomfort in the same participants (Figure 3). The difference in heat perception between cocaine and lidocaine administration first became statistically significant when esophageal temperature increased above 37.0°C and became larger as esophageal temperature progressively increased ($P < 0.05$) (Figure 3).

DISCUSSION

Although hyperthermia increases the risk for death after cocaine administration, the underlying mechanisms mediating cocaine-induced hyperthermia are poorly understood. The thermogenic properties of cocaine have been attributed largely to a hypermetabolic state that increases heat production. In contrast to this traditional view, our study shows that impaired heat dissipation is another major mechanism by which cocaine elevates body temperature in humans. When healthy cocaine-naïve persons were subjected to passive heating, pretreatment with even a small dose of intranasal cocaine impaired sweating and cutaneous vasodilation (the major autonomic adjustments to thermal stress) as well as heat perception (the key trigger for behavioral adjustments).

Figure 2. Effects of cocaine on autonomic adjustments to heat stress.



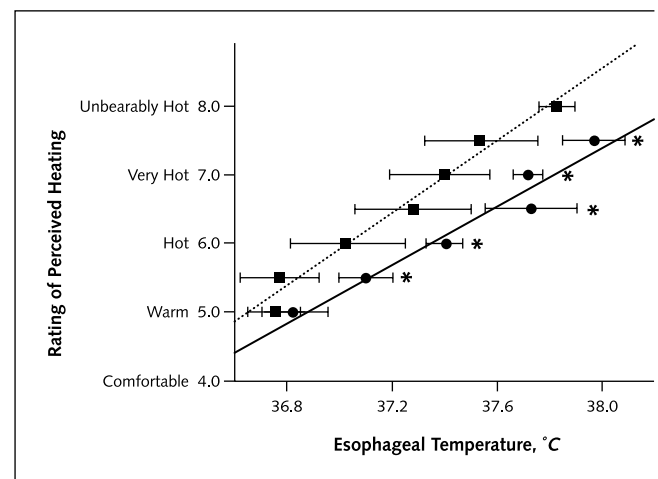
Solid lines indicate cocaine; dotted lines indicate lidocaine. Data are the mean (\pm SE). * $P < 0.01$ for cocaine vs. lidocaine.

When a person experiences repeated bouts of heat stress, the threshold temperature for the onset of sweating is remarkably constant, with an average test–retest variability of $0.09\text{ }^{\circ}\text{C}$ (15). During the passive heating used in our experiments, even a small dose of intranasal cocaine elevated the threshold for both sweating and cutaneous vasodilation by more than three times this

value, thereby markedly augmenting the increase in core temperature. That skin temperature increased similarly during both cocaine and lidocaine administration indicates that the thermal stress was equivalent under both conditions. In the absence of external heat stress, cocaine did not affect core temperature, suggesting that impaired heat dissipation (rather than augmented heat production) was the dominant mechanism underlying cocaine's hyperthermic properties. This pattern of cocaine-induced hyperthermia after exposure to heat stress resembles hyperthermia caused by impaired sweat gland function in patients with hereditary ectodermal dysplasia (16, 17), poisoning by muscarinic receptor antagonist (18), or growth hormone deficiency (19). However, the slope of the line relating increased sweating to increased core temperature was markedly reduced in these conditions (16, 19) but was unaffected by cocaine in our study, suggesting differences in pathogenetic mechanisms.

The precise mechanism by which cocaine impairs cutaneous vasodilation and sweating is still unknown. Both peripheral and central neural mechanisms could be involved. For example, cocaine is thought to inhibit the peripheral norepinephrine transporter, thereby increasing the norepinephrine concentration in the synaptic cleft (20). During thermal stress, augmented α -adrenergic vasoconstrictor tone in the cutaneous bed could contribute to the delayed onset of vasodilation. Inhibition of

Figure 3. Effects of cocaine on thermal perception.



Solid lines indicate cocaine; dotted lines indicate lidocaine. Data are the mean (\pm SE). The ratings of perceived heating were modified from reference 10. * $P < 0.05$ for cocaine vs. lidocaine.

norepinephrine reuptake, however, cannot explain the delayed onset of sweating during cocaine; sweating is regulated not by noradrenergic fibers but rather by sympathetic cholinergic fibers (9, 21).

The most plausible explanation for this mechanism is that cocaine-induced shifts in the threshold for cutaneous vasodilation and sweating are mediated centrally. This notion is consistent with recent findings indicating that cocaine acts centrally to stimulate sympathetic vasoconstrictor drive (11). We previously showed that under normothermic conditions, the dose of intranasal cocaine used in the current study increases sympathetic vasoconstrictor drive targeted to both the skeletal muscle and cutaneous beds (11). Our current data suggest that cocaine produces a distinctive pattern of altered central sympathetic outflow: augmentation of vasoconstrictor pathways accompanied by attenuation of active vasodilator and sudomotor pathways. This unique property of cocaine is not shared by other sympathomimetic drugs, such as methamphetamine and ephedrine, which cause hyperthermia mainly by increasing skeletal muscle metabolism and thermogenesis (22, 23).

In our current study, cocaine impaired the perception of heat stress; this is the most clear-cut evidence that cocaine acts centrally to alter thermoregulatory responses. This impairment was dramatic: Participants experienced less thermal discomfort with cocaine even though core temperature was higher than with lidocaine. We should emphasize, however, that this effect was observed with a very low dose of cocaine that did not produce euphoria (11). Larger doses of cocaine that produce intoxication, agitation, and increased locomotor activity would be expected to increase heat production, thereby compounding the hyperthermic effects of impaired heat dissipation. Furthermore, impaired heat perception would impair behavioral responses to hyperthermia, such as seeking a cooler environment or adjusting the thermostat on the air conditioner. In humans, these behavioral responses have the most powerful thermoregulatory effects (9).

We speculate that when recreational doses of cocaine are taken in a warm environment, such as in hot weather, in crowded nightclubs, or at “rave parties,” the hyperthermic effects of the drug will be greatly amplified (6, 24, 25). Because our study was performed only in cocaine-naïve, healthy persons, the results may not be applicable to persons with long-term cocaine use. How-

ever, long-term exposure to cocaine does not produce tolerance to cocaine-induced hyperthermia in rodents and can even produce “reverse tolerance,” an augmented response (26–28). Although our findings provide a new explanation for cocaine-induced hyperthermia at the organ-systems level, the cellular and molecular mechanisms are unknown. Elucidating the precise molecular mechanisms of cocaine-induced hyperthermia could lead to identification of new drug targets that may reduce cocaine-related deaths.

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Grant Support: By the National Institutes of Health (HL-61388) (Dr. Crandall); the American Heart Association, Texas Affiliate (0060010Y) (Dr. Vongpatanasin); and the National Institute on Drug Abuse (RO-1 DA10064) (Dr. Victor).

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Potential Financial Conflicts of Interest: None disclosed.

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