Imaging of Cocaine-Induced Global and Regional Myocardial Ischemia

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Severe and often fatal cardiac complications have been reported in cocaine users with narrowed coronary arteries caused by atherosclerosis as well as in young adults with normal coronaries. We have found that in normal dogs cocaine induces severe temporary hypoperfusion of the left ventricle as indicated by a significantly lower ^{201}Tl concentration compared to the baseline state. The most significant decrease in uptake occurred 5 min after injection and was more pronounced in the septal and apical segments. Following intravenous administration of cocaine, instead of gradual disappearance of ^{201}Tl from the left ventricle, there was continuous increase in ^{201}Tl concentration in the left ventricle. These imaging experiments indicate that the deleterious effects of cocaine on the heart are probably due to spasm of the coronaries and decreased myocardial perfusion. Since spasm of the large subpericardial vessels does not seem to explain the magnitude of the increased coronary resistance and decreased coronary flow after cocaine as described in the literature, it is suggested that microvascular spasm of smaller vessels plays a major role in the temporary decrease in perfusion. The data may also suggest that severe temporary myocardial ischemia is probably the initiating factor for the cardiac complications induced by cocaine.

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Evidence on the deleterious effects of cocaine on cardiac function is rapidly accumulating. Myocardial infarction (*1–8*), severe tachyarrhythmias (*2,8,9*), and sudden deaths have been attributed to cocaine (*10*). Case reports on cocaine-related deaths and summary review articles on the clinical and angiographic findings (*3,8*), as well as recent studies in volunteers with known cocaine-abuse histories, have been published (*11*). Most patients in whom severe or fatal "cocaine-related" cardiac manifestations developed had pre-existing atherosclerotic coronary artery narrowings (*4*); however, young cocaine users with normal coronary arteries who developed acute myocardial infarction were also described (*6,7*). The mechanism underlying the effects of cocaine on the heart is unknown. The cardiotoxic effects of cocaine are believed to be related to blocking of norepinephrine/serotonine (NE/SE) transporter sites by cocaine, preventing reuptake of catecholamines in the synaptic cleft, similar to the blocking of dopamine reuptake in the brain. The localized accumulation of catecholamines causes a generalized increase in sympathetic tone, resulting in tachycardia, rise in blood pressure, vasospasm and arrhythmias, as well as other symptoms of sympathetic overstimulation (*4*). Using autoradiographic microimaging techniques, we demonstrated that cocaine accumulates rapidly in the heart in high amounts (*12*). The vasoconstricting effect of cocaine is well known from observations on cocaine applied topically for local anesthesia and from studies on isolated vascular rings (*13*). Evidence of cocaine-induced vasospasm in the myocardium, however, is limited to measurements of physiological data such as the cocaine-induced increase in coronary resistance, increased myocardial oxygen extraction and decreased coronary flow (*14*). However, angiographic studies in humans given cocaine solution intranasally showed only minimal spasm of the subepicardial vessels, which did not match the much more significant reduction in coronary flow and the increase in coronary resistance (*15*). Electrocardiographic monitoring of cocaine abusers showed ischemic changes in some and nonspecific changes in others (*16*).

We hypothesize that the cardiac effect of cocaine is mainly by spasm of the coronary intramural microvasculature. To test this hypothesis we measured the relative myocardial perfusion in dogs with and without administration of cocaine, and confirmation studies with dual isotope microspheres were performed prior and after cocaine administration.

MATERIALS AND METHODS

Studies were performed in six adult mongrel female dogs (average weight ~36 lb). The protocol was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC). After pentothal anesthesia (28 mg/kg body weight), 74–148 MBq (2–4 mCi) ^{201}Tl-chloride (SYNCOR International Corporation, NY) was given intravenously, and the data were collected using

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a gamma camera. Static 5-min images were obtained in the anterior projection (with reference to supine dogs central axis) at 5, 20, 60, 120, and 180 min after injection. This protocol was considered as the baseline control for repeat studies performed with cocaine 7–10 days later using the same acquisition parameters. In the repeat experiments extreme care was taken to use similar conditions to the baseline studies (camera distance, angle, anatomical landmarks). An intravenous injection of 2 mg/kg body weight cocaine (this dose was selected based on literature data normalized to quantities of cocaine taken by human users) was followed 5 min later by ^{201}Tl using the same acquisition parameters as in the baseline state. Thus, each animal served as its own control for the cocaine study. In some animals the sequence was reversed, i.e., they were first studied with cocaine. Thallium-201 was chosen for these studies because the ultimate goal was to perform similar noninvasive evaluations in human users of cocaine by scintigraphy. The microsphere studies cannot be performed noninvasively in humans and in this case were used for validation purposes.

Electrocardiographic and clinical signs were monitored throughout the study (heart rate, blood pressure). Thallium-201 accumulation in the left ventricle (LV, global), in the septum (SPT), apex (APX), and lateral wall (LAT) were determined from the raw digitized images (128 × 128 matrix). Regions of interest (ROIs) were drawn manually by three independent observers and average counts in LV, SPT, APX, LAT in each segment were determined. Results were expressed as percentage of counts in the LV in the baseline 5-min image (100%), and all other values were normalized accordingly. Thallium-201 stress/redistribution programs available for analysis of clinical human thallium studies were used for comparison of the baseline controls versus cocaine image pairs at 5, 20, 60, 120, and 180 min. Approximately 100 μCi Co-57-labeled microspheres (15-μm diameter) were injected into the left atrium of three dogs. Five minutes later, a dose of 2 mg/kg cocaine was given intravenously, and after an additional 5 min, 100 μCi of ^{113}Sn-labeled microspheres (15 μm) were injected into the left atrium. The animals were killed 5 min later with pentothal overdose, the hearts were excised and ^{57}Co and ^{113}Sn radioactivity in the heart slices was determined for each isotope in a gamma-type well counter. The counts were corrected for any spillover of radioactivity and percent injected dose per gram of tissue were determined.

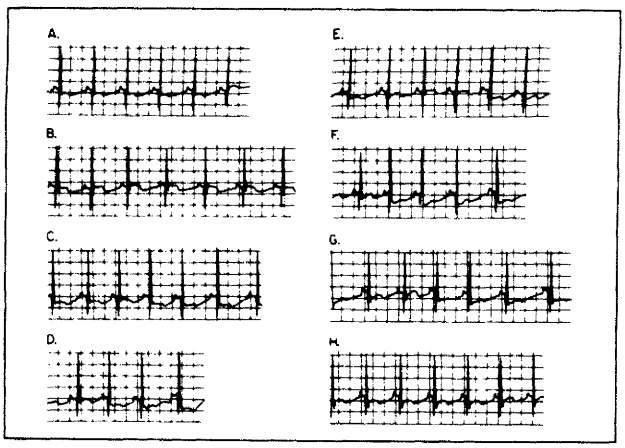

FIGURE 1. EKG tracings before (A) and following cocaine (B). Note progressive S T-segment depression and gradual recovery. Note: The tracings in the baseline state (A) is considered normal in the dog. A = baseline; B = Immediate post-cocaine injection (p.i.); C = 3 min p.i.; E = 5 min p.i.; F = 20 min p.i.; G = 60 min p.i., and H = 120 min p.i.

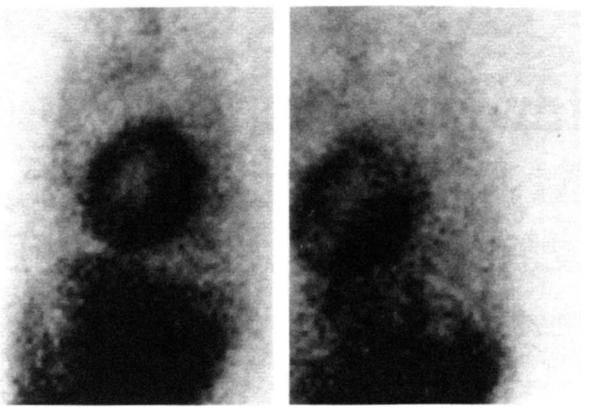

FIGURE 2. Thallium-201 scintigraphy in the dog. Right panel: ^{201}Tl injected 5 min after cocaine. Left panel: no cocaine was given. Notice higher and uniform ^{201}Tl concentration in the LV in the control state (right panel).

RESULTS

Cocaine administration caused significant ST-segment changes (Fig. 1) (ST depression of more than 2 mm and lasting about 20 min), but the pulse rate was not markedly affected. Figure 2 shows the raw ^{201}Tl images in the baseline state and after cocaine administration. The post-cocaine image has less activity compared with baseline, mainly in the septal region. In the baseline studies, maximal ^{201}Tl LV concentration was seen 5 min after ^{201}Tl injection with gradual washout over the 3-hr observation period, to approximately 65% of the initial values (Fig. 3c). After cocaine administration, global LV ^{201}Tl activity 5 min after injection was approximately 40% of the control 5-min values (Fig. 3b, d). Visual inspection of images after cocaine showed that in most animals the decrease in ^{201}Tl concentration was more marked in the septal and apical areas with appearance of "perfusion defects" similar to the exercise-induced ischemic defects observed in humans with coronary artery disease (Figs. 2 and 4). Following cocaine, there was a gradual increase ("washin") of ^{201}Tl in the LV (Fig. 2D) as opposed to the "washout" observed in baseline experiments without cocaine (Fig. 2C). In time, gradual filling-in of "perfusion defects" occurred (Figs. 4 and 5). Confirmation experiments using radiolabeled microspheres indicate that cocaine causes significant reduction in perfusion of the left ventricle and septum. The baseline/cocaine blood flow ratios were found to range from 9 to 16 in LV and 13 to 100 in septal regions.

DISCUSSION

We have shown that an acute intravenous dose of cocaine causes a profound decrease in global LV perfusion

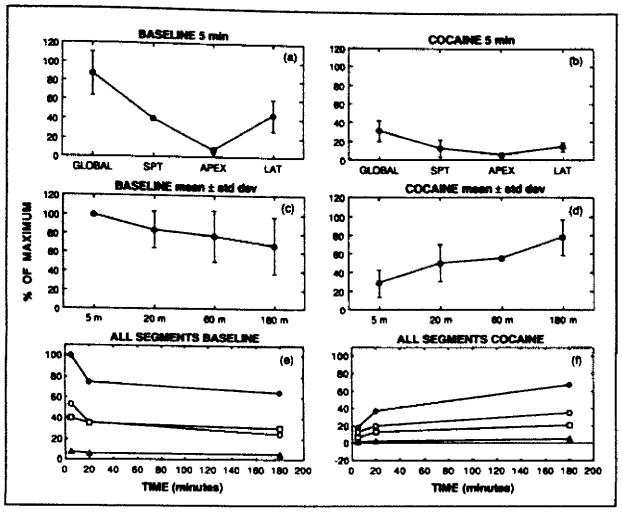

FIGURE 3. Mean ± s.d. of ^{201}Tl concentration in global LV, septum (SPT), apex, and lateral (LAT) walls expressed as percentages of maximum global ^{201}Tl activity in the baseline state. (a) Global and regional distribution of ^{201}Tl 5 min after injection and (b) when cocaine was injected 5 min before ^{201}Tl and images were obtained 5 min after ^{201}Tl. Notice significant decrease in global and regional ^{201}Tl activity. Time-activity curves of global ^{201}Tl in baseline state (c) and after cocaine (d). Thallium-201 washes out in baseline (c) and increases in time after cocaine (d). The different time-activity curves occur in the global LV as well as in each segment (curves e and f), ○ = Global, ◇ =Lateral, □ = Septal, △ = Apical.

with appearance of regional "perfusion defects" in the septum and/or apex. Cocaine apparently causes increased oxygen demand which in normal animals is met by vasodilation. In the presence of cocaine, however, vasodilation is not occurring and on the contrary spasm is prominent, probably decreasing coronary flow (*14,15*).

In humans, a global decrease in LV ^{201}Tl uptake after injection at peak exercise is believed to represent the effect

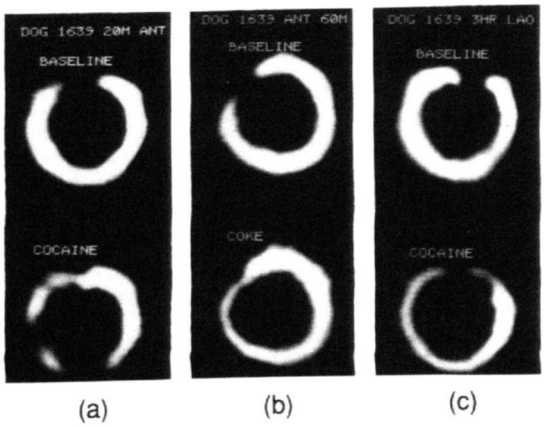

FIGURE 4. Computer-processed ^{201}Tl scintigrams of canine LV. Notice uniform distribution of ^{201}Tl in baseline studies (upper row) compared to appearance of perfusion defects after cocaine (lower row) in septum and apex with gradual partial reperfusion (a = 20 min, b = 60 min, c = 180 min).

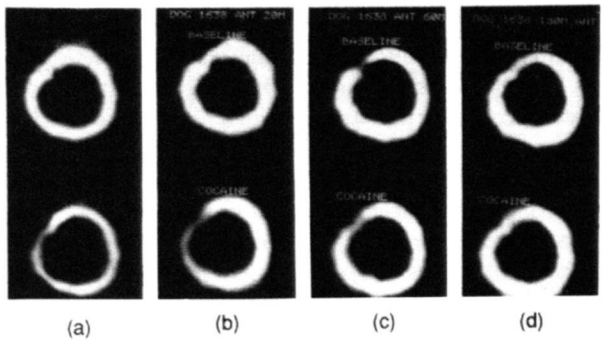

FIGURE 5. Septal and apical hypoperfusion is also noted as a narrowing of the band of activity in another dog administered cocaine, followed by complete reperfusion (a = 5 min, b = 20 min, c = 60 min, d = 180 min).

of triple-vessel coronary artery disease. The magnitude of the decrease in LV uptake following cocaine in dogs without fixed coronary artery narrowings is remarkable and can only be indicative of generalized severe temporary coronary artery spasm. Angiographic studies in dogs and in humans (*15*) have failed to demonstrate severe spasm in the large subepicardial coronary arteries after cocaine. Thus, our data with ^{201}Tl and microspheres are in accordance with the reduction in coronary flow and increased resistance indicating that the phenomena is a summation of the subepicardial and intramural vascular spasm. It must be therefore assumed that the decrease in the LV ^{201}Tl concentration is due to a combination of factors, including spasm of smaller vessels not visualized by angiography, possibly the intramyocardial microvasculature ("resistance vessels"), as well as some degree of spasm of the subepicardial arteries (*16*). The maximal difference in LV ^{201}Tl concentration between baseline and after cocaine, occurs very early after cocaine injection. Thereafter, there is a gradual increase in counts over the LV, indicating a return of the normal circulation and possibly reactive hyperemia, which often follows vasospasm. The initially decreased concentration of LV ^{201}Tl following cocaine with gradual return to baseline values after 3 hr was observed in the global LV as well as in the segmental values. However, the initial decrease in LV ^{201}Tl uptake was not uniform, the septal and apical segments being more affected than the lateral wall. This nonuniform effect of cocaine on myocardial perfusion is interesting but the reasons for these regional differences are not yet clear. Regional differences in cocaine binding receptor densities may be one of many possibilities. It was also previously shown that under increased LV pressure work, there may be different effects on the perfusion in the endocardium versus epicardium and in the free wall versus septum (*17,18*). A decrease in metabolism and in perfusion especially in the septum in hypertensive myocardium was described (*19*). It appears that the vasospasm in the coronary vessels is probably more pronounced than the increased oxygen demand induced by cocaine (*14*). The

effects of cocaine bear some resemblance to that of patients with angina pectoris and normal coronary arteriograms, in some of which spasm could be demonstrated by decreased coronary flow and increased resistance, a condition termed "microvascular angina" (*20*). In this syndrome, and apparently also after cocaine, myocardial ischemia occurs despite angiographically normal or near-normal subepicardial coronary arteries. In this situation, ^{201}Tl scintigraphy thus probably represents the small vessel spasm which is not so evident on angiography. It is reasonable therefore to speculate that the mechanism of cocaine-related myocardial ischemic events in individuals with normal coronaries may therefore be caused by microvascular spasm.

These findings corroborate with our earlier observations showing that, after intravenous injection, there is rapid accumulation of cocaine in the heart, brain and adrenals (*12*). The vasospastic effect of cocaine observed in anesthetized animals may be different from that in unanesthetized animals. It is not known if the effect of cocaine is mediated through the brain or is a direct effect on the peripheral organs, i.e., heart and blood vessels. It is known that pentothal anesthesia "blunts" the effect of sympathomimetics. Thus, after cocaine tachycardia and rise of blood pressure were not as prominent as in the conscious animals. Using ^{201}Tl scintigraphy and imaging, which began 5 min after injection, dictated the immediate use of anesthesia. In a limited number of experiments, cocaine was given and ^{99m}Tc-MIBI$_6^+$ (Cardiolite, E.I. Du Pont) was injected 5 min later. The dogs were anesthetized and scanned 1 hr later with similar results as in the anesthetized dogs. This method has the advantage of slower redistribution of Cardiolite as compared to ^{201}Tl. Individuals with fixed narrowings of coronary arteries in whom microvascular spasm develops after cocaine, will experience an amplified effect caused by the fixed narrowing of the subepicardial coronary arteries, and the additional intramyocardial microvascular spasm.

It appears that the initiating factor in acute cocaine "cardiotoxicity" is probably the profound global and regional left ventricular vasospasm causing ischemia. A more quantitative protocol of ^{201}Tl scintigraphy may be useful for evaluating agents that prevent or relieve coronary vasospasm. In addition, given the noninvasive nature of the procedure, the study may also prove useful in monitoring the effects of treatment in patients with cocaine-related cardiovascular complications. Sequential scinti-imaging and determination of the rate of LV ^{201}Tl "washin" or "washout" may provide information on the degree and subsequent relief of coronary vasospasm and assist in monitoring the effect of treatment. It may also be worthwhile to evaluate the ^{201}Tl scintigraphic method in patients with microvascular angina in the baseline state and after provocation tests with ergonovine to image the intramural coronary artery vasospasm possibly responsible for the episodic chest pain in these patients.

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