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# Myocardial Hypertrophy and Coronary Artery Disease in Male Cocaine Users

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**ABSTRACT:** We compared the heart weights and the incidence of atherosclerotic lesions in trauma fatalities testing positive for cocaine with the hearts of cocaine negative trauma fatalities, with the hearts of decedents dying from cocaine overdose, and with historic controls derived from the literature. There were 116 trauma victims, 83 men and 33 women, aged 20–50 years, and 26 men with cause of death listed as cocaine toxicity. The 32 cocaine (+) male trauma fatalities had a mean age 34 ± 10 years and a mean heart weight of 375 ± 82 grams. The 51 cocaine free males had a mean age 31 ± 9 years, and mean heart weight 337 ± 54 grams ($P$ = .01). Heart weights in the cocaine using group were also significantly greater than historical controls from World War I, Korea, and Vietnam. The incidence of atherosclerotic changes was similar in both groups, but cocaine (+) men had more frequent coronary artery lesions involving multiple vessels ($P$ = .01). Comparisons between 16 cocaine (+) females and 17 cocaine (−) female controls disclosed no significant differences in heart weight or the frequency of atherosclerotic lesions. The 26 men dying of cocaine overdose also had larger hearts than the controls (379 ± 64 g, $P$ = .004), and more severe CAD (30% had involvement of 2 or more vessels, $P$ = .02). The degree of myocardial hypertrophy documented in this study was highly significant, but because the increase is modest (around 10%), it is likely to go unrecognized at autopsy. Cardiac enlargement and coronary artery disease in cocaine users may be much more prevalent than has previously been appreciated, and may be responsible for some unexplained cases of sudden death in cocaine users.

**KEYWORDS:** pathology and biology, cocaine, myocardial hypertrophy, coronary artery disease

Coronary artery disease and left ventricular hypertrophy are established risk factors for sudden death in cocaine users [*1*]. Mounting laboratory, clinical, and experimental evidence suggests that both abnormalities may actually be a direct consequence of chronic cocaine use [*2–5*]. If that is the case, then the number of relatively young people at risk for sudden death, as well as the other consequences of myocardial enlargement and coronary artery disease, may be much higher than previously has been appreciated.

Assessing the magnitude of the problem in asymptomatic young people is difficult. In the past, the incidence of asymptomatic heart disease in young adults has been approximated by studying the hearts of soldiers killed in combat [*6–8*]. But even in peace time, trauma is still the most common cause of death for American males under the age of 40, and a large percentage of these patients are under the influence of drugs when their injuries are sustained [*9,10*]. We compared the hearts of individuals dying from traumatic injuries, who also happened to be cocaine users, with the hearts of trauma fatalities who were not using cocaine at the time of their fatal injury. We found very important differences.

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## Materials and Methods

### *Site*

The Clark Country Coroner-Medical Examiner's office serves a population of just under 1,100,000. with approximately 4000 cases evaluated by the Medical Examiner each year. Only patients age 20–50, with complete autopsies and toxicology testing, done from from January 1, 1993 to March 1, 1994, were included in the study. All of the autopsies were performed by the same two pathologists, with one pathologist having done 66% of the examinations (GSG). Neither pathologist was aware of the decedents drug history at the time of the autopsy.

### *Comparison Groups*

Patients testing positive for other stimulant drugs were excluded. Patients with penetrating heart injuries were included, provided that they had not undergone surgery just prior to death. A third study group consisted of 26 men whose deaths were found to be the result of cocaine toxicity. The control group was comprised of patients meeting similar criteria but who had no cocaine, cocaine metabolite, or stimulant drugs detected, and who had not been harvested for organ donation. The mechanism of injury for the two different groups is shown in Table 1. Body weight and heart weights for each patient were recorded, as was a description of the aorta and coronary arteries.

### *Autopsy Technique*

The pulmonary trunk and ascending aorta were excised roughly one inch above the sinotubular junction. Parietal pericardium and intracavitary clot were removed, but pericardial fat was left intact. Hearts were weighed on a Mettler balance immediately after they were removed from the chest. The degree of coronary artery atherosclerosis was estimated through five or six transverse incisions along the course of each of the major epicardial vessels.

TABLE 1—*Mechanism of injury for all, male and female, cocaine positive and cocaine negative decedents.*

| Mechanism of Injury | Cocaine Positive ($n$ = 48) | Cocaine Negative ($n$ = 69) |
|---|---|---|
| Gun shot wounds | 21 (44%) | 40 (57%) |
| Stab wound | 11 (23%) | 4 (6%) |
| Strangulation | 5 (10%) | 2 (3%) |
| Motor vehicle accident | 4 (8%) | 10 (15%) |
| Auto-pedestrian | 4 (8%) | 1 (1%) |
| Fall from height | 1 (2%) | 2 (3%) |
| Drowning | 1 (2%) | 0 (0%) |
| Assault | 1 (2%) | 6 (9%) |
| Plane crash | 0 (0%) | 4 (6%) |

### *Toxicology Testing*

Urine and blood were available for most cases. Toxicology screening was done with commercial immunoassay kits. All positive test results were confirmed using standard GC/MS techniques. Individuals were considered positive for cocaine so long as any cocaine, or cocaine metabolites, were detected in the urine or blood.

### *Statistical Analysis*

Measured heart weights in cocaine positive and in cocaine negative groups, were compared, and these compared, in turn, to predicted heart weights using the generally accepted formula of 0.4% × body weight for men and 0.45% × body weight for women [*11*]. Observed heart weights for drug positive and negative groups were also compared to predicted heart weights based on the Mayo Clinic nomogram [*12*]. The unpaired Student's t test was used to test for significant differences between sample means. The Chi-square test was used for analysis of coronary artery lesions in the drug negative and positive groups. For all the tests a probability value of $<0.05$ was considered significant.

## Results

### *Age*

Mean age for the cocaine positive male trauma patients was 34 ± 9 years, and mean age for the male controls was 31 ± 8.5. Cocaine positive women had a mean age of 32 ± 9 years while the controls were 33 ± 9 years. The 26 men dying from cocaine toxicity was slightly older, with a mean age of 36 ± 7 years.

### *Body Weights*

The mean weight for the control men was 80.6 kg ± 16.3 grams. The mean weight for the cocaine using trauma patients mean was 76.6 kg ± 11.6 kg, not significantly different from the controls ($P$ = .1049). The mean weight for the 26 men with cocaine listed as cause of death was 79.1 kg ± 18.7 which, again, was not significantly different from the control group ($P$ = .709).

### *Heart Weights*

Mean heart weight in the 32 men testing positive for cocaine was 375 grams (±82, SE = 11.1), less than the generally accepted value of 380 grams many clinicians use as the cut off value for normal in men (350 grams in women), but significantly more ($P$ = .01) than the 337 grams (±55, SE = 7.6) in the control group. Histograms of the weights for cocaine positive and negative groups are shown in Figs. 1 and 2. It is apparent that two different populations are described, and that the distribution of cocaine users heart weights is positively skewed.

Heart weights of subjects in the cocaine-free control group were compared with heart weights predicted by the Mayo Clinic nomogram, and also with the results of the 0.4% × body weight formula. There was no significant difference between the observed and predicted heart weights with either method of calculation (Mayo Clinic nomogram = 347 grams predicted weight vs. 337 gram observed weight ($P$ = .276); 0.4% × body weight = 323 grams predicted weight and 337 grams observed weight ($P$ = .214). Applying the same .4% factor to the male cocaine users, the predicted heart weight would have been only 306 grams versus the observed weight of 374 grams. The difference was highly significant ($P < .0001$). Predicted heart weights were calculated for the cocaine positive group using the Mayo Clinic formula and the difference remained highly significant (374 grams vs. 341 grams, $P$ = .0062).

The mean heart weight of the 16 women in the cocaine positive group was 303 grams ± 89 grams, SD = 22.3), while the mean

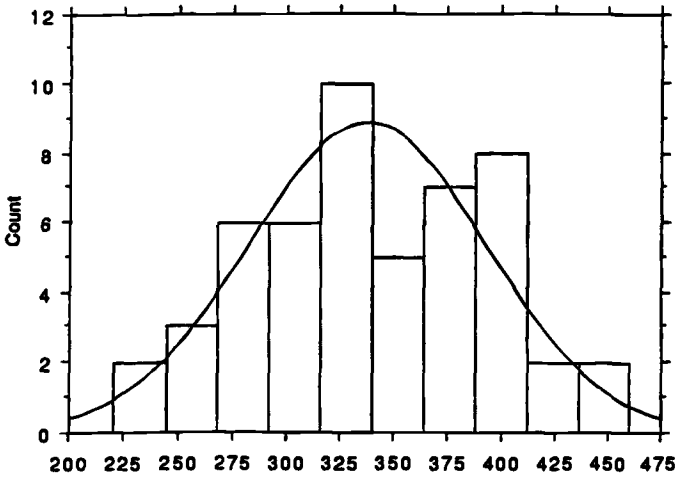


FIG. 1—*Heart weight histogram for cocaine-free trauma patients. Note normal distribution.*

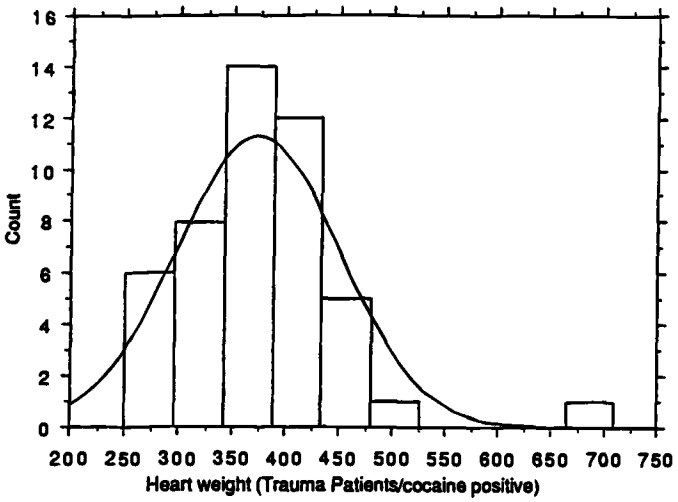


FIG. 2—*Heart weight histogram for cocaine-positive patients. Note that distribution is positively skewed.*

heart weight of the 17 women in the control group was 257 ± 62 grams, SD = 15). The differences between the cocaine positive and cocaine negative women did not achieve significance ($P$ = .09). The observed heart weights of the control women were as predicted by the Mayo Clinic nomogram (257 grams observed, 266 grams predicted, NS). Heart weights of the cocaine using women were not significantly different from predicted weights by either formula. The 26 men dying of cocaine toxicity had mean heart weights of 379 ± 64 grams, significantly more than the mean for the male trauma controls 337 ± 55 grams ($P$ = .004), significantly more than predicted by the .4% formula ($P$ = .002), and significantly more than predicted by the Mayo Clinic nomogram ($P$ = .02).

*Coronary Artery Disease*

More multiple vessel coronary artery lesions were noted in the male cocaine users than in the male controls ($P$ = .01). Twenty five percent of the cocaine users had lesions in 2 or more vessels, but only 6% of the controls had 2 vessel involvement, and none of the controls had 3 or 4 vessels involved. Table 2 shows the findings in the cocaine negative and positive groups.

The frequency of coronary artery lesions was the same in female cocaine negative and cocaine positive fatalities. Seventy percent of the controls and 50 percent of the cocaine users had no lesions. Eighteen percent of the controls and 25 percent of the cocaine group had aortic fat streaks. One cocaine using woman had three vessel disease and another had lesions in one vessel. One control patient had two vessel involvement. The difference did not attain statistical significance. The 26 men with cocaine toxicity also had significantly more atherosclerotic lesions than the controls. Only 6% of the controls had lesions in 2 or more vessels, but such lesions were present in 30% of the cocaine group ($P$ = .02).

*Comment*

Cocaine users with coronary artery disease, left ventricular hypertrophy, or both, are at increased risk for sudden death [*13*]. Cocaine causes coronary artery spasm [*14,15*], but death can result even in the absence of spasm. Fixed lesions have been found in more than half of the reported cases of cocaine related myocardial infarcts [*16*], and the relative contribution of spasm and fixed lesions remains unclear. However, the presence of underlying coronary artery disease certainly places users at increased risk. Left ventricular hypertrophy is also a recognized, blood-pressure-independent, risk factor for sudden death in the general population [*17*].

TABLE 2—*Frequency of coronary artery lesions in male cocaine and male controls groups. None of the controls had 3 or 4 vessel disease, but 19% of the cocaine positive men had involvement of 3 or more vessels (P = .01). The 26 patients dying of cocaine overdose also had significantly more multivessel disease than the controls.*

| | Cocaine (+) Trauma Deaths ($n$ = 32) | Cocaine (−) Trauma Death ($n$ = 52) | Cocaine Overdose Deaths ($n$ = 26) |
|---|---|---|---|
| No lesions | 18 (56%) | 24 (47%) | 5 (19%) |
| Aortic fat streaks | 5 (16%) | 15 (29%) | 10 (38%) |
| Lesions in 1 vessel | 1 (3%) | 9 (17%) | 4 (15%) |
| Lesions in 2 vessels | 2 (6%) | 3 (6%) | 2 (8%) |
| Lesions in 3 vessels | 4 (13%) | 0 (0%) | 4 (15%) |
| Lesions in 4 vessels | 2 (6%) | 0 (0%) | 1 (4%) |

*Myocardial Hypertrophy*

Our results confirm the occurrence of substantially increased heart weights in men, but not women. More research is needed to see if differences in women's heart weights would be found with a larger sample. Given the fact that cardiac enlargement has already been noted in cocaine users with sudden death [*18*], and that echocardiographic measurements of healthy, asymptomatic, cocaine detoxification patients have also shown increased left ventricular mass and posterior wall thickness [*19*], the findings of the current study are not entirely surprising. However, the nature of previous studies precluded conclusions as to whether cocaine actually caused cardiac enlargement, or whether it was a preexisting condition that placed the individual at greater risk for sudden death. Our autopsy findings confirms these earlier clinical studies.

Mean body weights in cocaine positive trauma deaths, and in the 26 men where cocaine was the cause of death, were not significantly different from body weights in the control group. However, heart weights were greater in cocaine using trauma fatalities than in controls, and they were also greater than historical controls. Conceivably the anorectic and sympathomimetic effects of cocaine could have resulted in lower body weights for the cocaine users, elevating the ratios of heart to bodyweight. However, since body weights were the same in both cocaine and control groups, the difference between observed and predicted weights must reflect a real increase in heart weight. The increase is also apparent when the heart weights observed in this study are compared with historical controls. A study of 105 Vietnam combatants, with a mean age of 22.1 years, found mean heart weights of 314 grams, not significantly different from the mean heart weight in our control group [*8*]. Seventy years ago Aschoff studied 468 World War I combat fatalities and found mean heart weights of 319 grams [*6*], essentially the same value recorded in Vietnam. Table 3 summarizes the heart weights of the historical controls.

There is no universally agreed way to determine "normal" heart weights, and several different systems are commonly used. Some pathologists use the arbitrary cut offs of 380 or even 400 grams for men and 350 grams for women, but others prefer to calculate heart weight as a percentage of body weight. Heart weights equal to less than 0.4% of the body weight are considered normal for men, while less than 0.45% is considered normal for women [*11*]. We used this formula to calculate predicted heart weights for our cocaine positive and negative groups and the predicted weight for the cocaine negative group (322 grams) was not significantly different than the observed weights (337 grams, $P$ = .213). However, in the cocaine positive group, the difference between observed (374 grams) and predicted (306 grams) was highly significant ($P$ < .0001).

Kitzman et al. characterized the weight and dimensions of 765 hearts from Mayo Clinic patients who were free of heart disease and derived a nomogram relating heart weight to body weight

TABLE 3—*Comparison of observed heart weights against historical controls. The weights listed below are for males only.*

| Year | # of patients | Mean Age | Heart Weight | Range | Refer # |
|---|---|---|---|---|---|
| 1924 | 468 | 29 | 319 | NA | #6 |
| 1942 | 300 | 21–50 | 319 | 200–424 | #30 |
| 1971 | 105 | 22 | 314 | 240–430 | #7 |
| 1993 | 51 | 31 | 337 | 190–450 | UMC Control |
| 1993 | 32 | 34 | 374 | 250–710 | UMC Cocaine |

[12]. We used his nomogram to calculate predicted heart weights for our decedents. Predicted mean heart weights in the control group were not significantly different than the observed mean weights (observed = 337 grams, predicted = 347 grams, $P$ = .276), but in the cocaine positive group the difference (374 grams vs. 341) was highly significant ($P$ = .0062).

Why cocaine use should cause myocyte hypertrophy is not known with any certainty, but chronic cocaine use results in elevated circulating levels of catecholamines [20], and excessive catecholamine stimulation can cause myocardial hypertrophy [21], even in the absence of significant hypertension. In spite of the significant difference between the cocaine users and controls, heart weights in both groups fell within ranges generally considered normal. Such increases are likely to go unnoticed. Since the increased weight in the trauma patients amounted to only a 10% increase, it is likely that even measurements of wall thickness probably would have fallen within normal limits. That, however, does not mean that this increase in mass is benign. The presence of myocardial hypertrophy is associated with subendocardial ischemia, abnormal impulse propagation and reentry arrhythmias [22]. When the other cardiotoxic effects of cocaine, including sodium channel blockade [23–25], increased myocardial work [24], and catecholamine mediated microfocal fibrosis [26] are then superimposed on such preexisting abnormalities, sudden death would not be such a surprising outcome.

### *Coronary Artery Disease*

Mönckeberg examined the aortas of combat fatalities in World War I and found that atherosclerotic lesions, both fat streaks and plaques, were present in 75.6% of soldiers who were under 25 years of age [6]. Fat streaks and fibrous thickening were found in 35% of the American fatalities in Korea [7], in 45% of those killed in Vietnam [8].

The incidence of atherosclerotic lesions was not significantly different in the cocaine negative and cocaine positive fatalities. Forty three percent of the control group, and 35% of the cocaine using group showed some evidence of atherosclerotic disease. However, the disease was much more severe in the cocaine users. None of the controls had three or four vessel involvement, but 6 of the cocaine users did ($P$ = .01). Most of the pathologic changes in the control group amounted to little more than prominent fat streaks and early plaques in the aorta (15/51 cases). A comparison of the findings is shown in Table 2. Compared to both our controls, or to the more recent historical controls from Vietnam, the incidence of coronary artery disease in our cocaine using group was high, and statistically significant.

A relationship between cocaine use and coronary artery disease was first suggested by Virmani in 1988 [26], and indirect evidence has continued to accumulate ever since. In one study, 60% of individuals with cocaine associated sudden death were found to have severe atherosclerosis, even though the average age was only 47 years [28]. In another autopsy study, the average age of patients with cocaine related thrombosis group was only 29 years, and the degree of luminal narrowing higher than would be anticipated in that age group [29]. Our findings confirm the findings of these earlier studies and suggest a causative relationship between cocaine use and accelerated atherosclerosis. The underlying mechanism for CAD in cocaine users remains obscure, but one line of evidence suggests that cocaine is directly toxic to endothelial cells, and that it favors intracellular calcium accumulation [5]. Catecholamine excess has also been suggested as a cause for accelerated atherosclerosis [31].

Our study has some obvious limitations. First, nothing can be inferred about individual patterns of cocaine use. A positive urine or blood test for cocaine metabolite simply means that cocaine was used within a day or so of death. A negative test just means that cocaine had not been used in the immediate perimortem period [30]. Still, it is reasonable to assume that if cocaine was present at the time of death, it probably had also been used repeatedly in the past. Secondly, nothing is known about the drug status of the historical controls. However, from 1920 to 1980, cocaine use in the United States was decidedly uncommon, and cocaine use by the historical controls seems extremely unlikely. Another difficulty involves the measurement of cardiac weight at necropsy. Variations can occur depending on the protocol used and on the prosector making the measurements. All of the autopsies in this study were carried out by the same two pathologists, who had no knowledge of the decedents drug history. Artifactual weight variations due to technique would not be expected under such circumstances.

The most serious problem concerns the nature of the observed increase in heart weight. Constraints imposed by limited staffing and a rapidly increasing case load prevent us from doing routine microscopic examinations of the heart. As has been previously reported [26,27], microscopic changes such as contraction band necrosis and fibrosis are frequent findings in the hearts of cocaine users. Additional autopsy studies are need to assess the frequency of these changes and their relative contribution to the increased heart weights reported here.

Without microscopic examination, and without recorded measurements of wall thickness, it could be argued that the increased heart weight is not the result of myocardial hypertrophy, but some other factor, such as epicardial fat accumulation, extensive fibrosis, or infiltrates. In response to such an objection, it should be noted that (1) the same two pathologists did all the examinations and, (2) that fat was never removed from the heart, and (3) no abnormalities, such as grittiness or discoloration were noted on the cut surface of the myocardium, as would be expected if there had been previous infarcts.

## Conclusion

Accelerated atherosclerosis and myocardial hypertrophy are both sequels of chronic cocaine use. Both are known risk factors for sudden death, and the presence of either or both abnormalities could explain many cocaine related deaths. The degree of myocardial hypertrophy documented in this study was highly significant. But, because the increase is modest (around 10%), it is likely to go unrecognized at autopsy. Cardiac enlargement in cocaine users may be much more prevalent than has previously been appreciated. While the incidence of coronary atherosclerosis in the cocaine group was no higher than in the controls, when disease was present it involved multiple vessels. Our observations support previous suggestions that cocaine use is, itself, atherogenic.

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