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# Myocardial necrosis and cocaine

## A quantitative morphologic study in 26 cocaine-associated deaths

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**Abstract** A quantification of different forms of acute myocardial necrosis, myocardial leukocytic infiltrates and myocardial fibrosis was accomplished in 26 chronic cocaine abusers who died of cocaine intoxication and compared to 45 normal subjects who died from head trauma and 38 who died of acquired immunodeficiency syndrome. The findings were: absence of infarct necrosis, a similar frequency and extent of coagulative myocytolysis (contraction band necrosis) and leukocytic infiltrates in cocaine abusers and normal controls, and an absence of myocardial fibrosis in cocaine abusers. These findings question both the acute and chronic cardiotoxicity of cocaine. The infarct-like pattern in some predisposed subjects may be due to an excess of catecholamine release induced by the drug resulting in coagulative myocytolysis and platelet thrombi.

**Key words** Cocaine · Necrosis · Contraction band necrosis · Myocarditis

## Introduction

The relationship between morphological background and cardiac disorders in cocaine abusers is still controversial. The present postmortem study has been carried out to define the types and to quantify the frequency and extension of myocardial necrosis, inflammatory infiltrates and myocardial fibrosis in 26 chronic cocaine abusers who died of cocaine intoxication. The quantification of the morphologic background of cocaine cardiotoxicity should help in defining its functional significance.

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## Materials and methods

### Study population

The chronic cocaine abusers were 26 cases of cocaine-associated death; 16 from the Dade County Medical Examiner Department, Miami, USA, and 10 from the Department of Forensic Sciences, Faculty of Medicine, University of Siena, Italy. Of these 18 died out of hospital and 8 died in hospital.

The controls subjects were 45 normal subjects who died almost instantaneously (26 cases) or after a survival time of 1–12 h following head trauma (19 cases) without postmortem evidence of any disease and 38 subjects who died from documented acquired immunodeficiency syndrome (AIDS) after a long stay in hospital. This control group was selected since AIDS patients, irrespective of concurrent opportunistic diseases show contraction band necrosis and lymphocytic myocarditis [1]. Toxicological tests were negative for all subjects. Of the latter 29 had a history of intravenous drug abuse, mainly heroin.

To avoid any possible interference between coronary atherosclerosis and myocardial changes, only chronic cocaine abusers and controls with no or minor (≤ 50% lumen-diameter reduction) coronary atherosclerosis were included in this study. In all cases no resuscitation attempts were done.

The method of heart examination has been reported previously [1]. In brief, in each case the heart was weighed, opened and inspected and any gross changes examined histologically. The coronary arteries were cross-sectioned at 3 mm intervals and any segment with luminal modification was processed for histology. Myocardial samples of the left anterior wall (n = 2–4) were systematically taken, fixed in 10% buffered formalin and embedded in paraffin. Histological sections were routinely stained with hematoxylin-eosin.

### Quantitative analysis

The myocardial area of each histological section was calculated in $mm^2$ by an image analysis system (Vidas, Zeiss). The slide image was digitized, the total myocardial area was measured in pixels and converted to $mm^2$ by a calibration procedure using a reference system. The following histological parameters were normalized to 100 $mm^2$:

1. Number of foci and myocells with coagulative myocytolysis.

2. Number of foci of intermyocellular lymphocythic infiltrates, with or without myocell necrosis and perivascular lymphocytic infiltrates.

Myocardial fibrosis was expressed as the percentage of the total histological area using an orthogonally bisected ocular.

## Definitions

The following form of myocell injury in relation to its function were differentiated [2–3]:

1. Infarct necrosis is the pathognomonic lesion found in myocardial infarction. The myocell stops functioning by irreversible relaxation and the first histological sign (already visible within 1 h) is elongation of nuclei and sarcomeres as a consequence of stretching of myocardial fibers by intraventricular pressure with paradoxical bulging (atonic death) (Fig. 1). Polymorphonuclear infiltration, secondary thrombosis of intramural vessels, macrophagic digestion of dead tissue within sarcolemmal tubes and collagenization are successive stages of this usually monofocal lesion which ends in massive scar tissue.

2. Coagulative myocytolysis (or contraction band necrosis) is a plurifocal, mainly microfocal lesion, which begins with irrever-

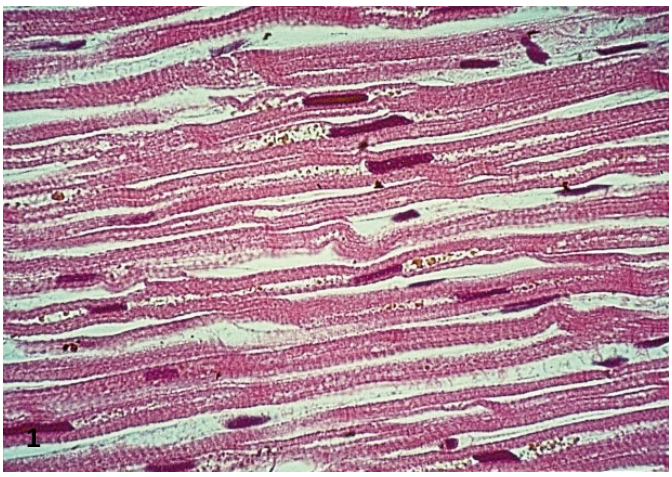
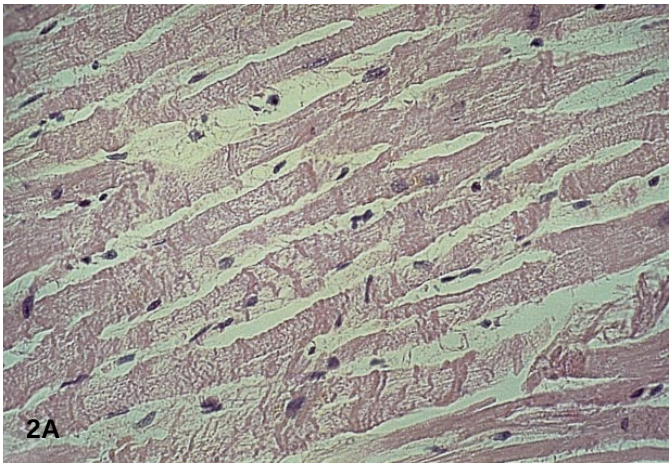
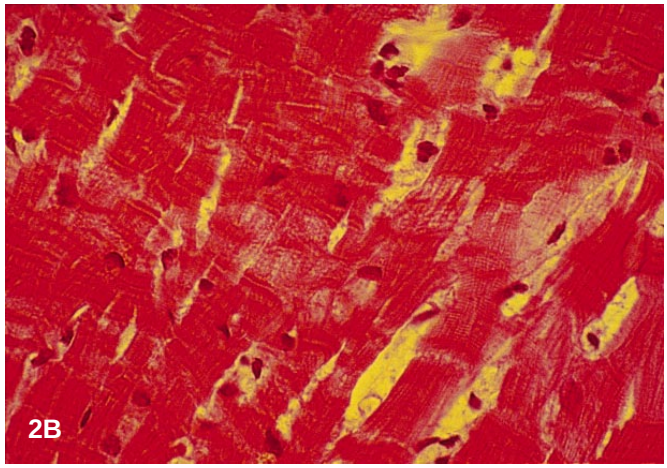
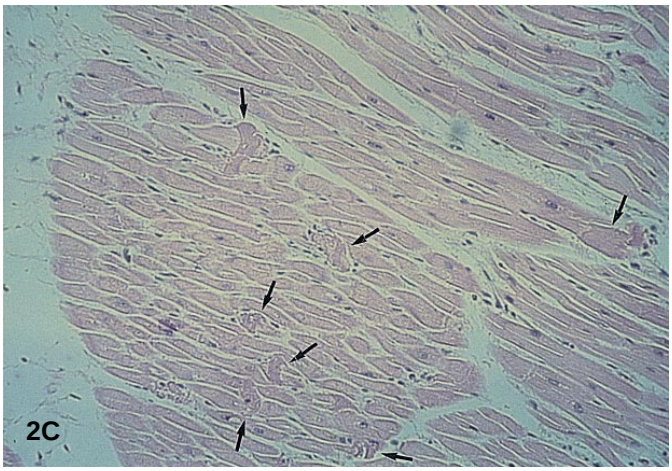


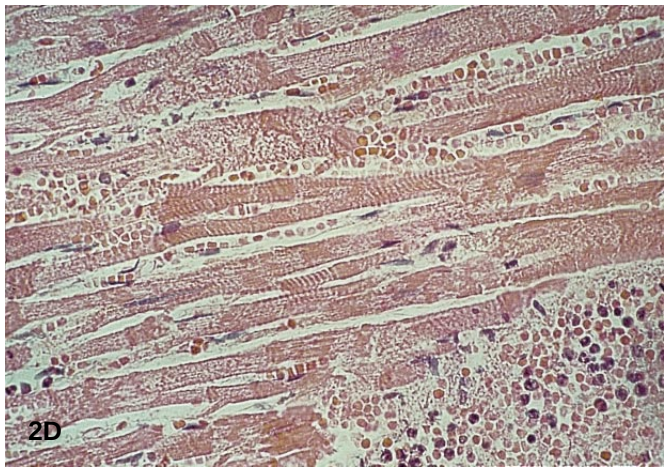

**Fig. 1** Early phase of an acute myocardial infarction in 56-year-old man. Stretching of the non contracting myocells by intraventricular blood pressure results in elongation of sarcomeres and nuclei (H & E × 250). A finding never observed in our cases of cocaine abusers

**Fig. 2A** Fragmentation of the entire myocell (pancellular lesion) in anomalous cross bands formed by segments of hypercontracted sarcomeres and myofibrillar rhexis in a 34-year-old AIDS patient (H & E × 250). **B** A small focus of coagulative myocytolysis in a 28-year-old male cocaine addict who survived a few hours after a cocaine intoxication.This very early lesion shows a focus of hypercontracted myocells with band formation and minor rhexis of myofibrils. (H & E × 250). **C** A 31-year-old male cocaine addict showing paradiscal lesion involving 10–15 hypercontracted sarcomeres adjacent to the intercalated disc. The major portion of the myocell is normal. (H & E × 100). **D** Reflow necrosis in the left anterior papillary muscle in a 25-year-old male cocaine addict (H & E × 250). This lesion diverges from typical coagulative myocytolysis since extensive anomalous bands are associated with massive interstitial hemorrhage



sible hypercontraction of the whole myocell (tetanic death) and consequent myofibrillar rhexis with anomalous deeply eosinophilic cross-bands formed by hypercontracted sarcomeres with marked thickening of Z-lines. This fragmentation is probably due to the action of adjacent and normally contracting myocells on rigid, hypercontracted elements (Fig. 2A and B). Three evolutive aspects can be recognized:

a. Hypercontraction/cross-bands.

b. Alveolar formed by empty sarcolemmal tubes with macrophages containing lipofuscins.

c. Healing, i.e. progressive collagenization with macrophages and fibroblasts. This pancellular lesion is often associated with a paradiscal lesion formed by a unique band of 10–15 hypercontracted sarcomeres adjacent to the intercalated disc (Fig. 2C). Myofibrillar rhexis is not likely because most of the myocell is morphologically and functionally normal. Both pancellular and paradiscal lesions are induced experimentally by intravenous infusion of catecholamines [4–5] apparently without relation to ischemia.

3. Myocardial reflow necrosis is a variant of coagulative myocytolysis associated with massive hemorrhage (Fig. 2D). A pattern seen after temporary severe ischemia. Infarct necrosis and pancellular coagulative myocytolysis were defined acute at any stage of their evolution until the healing phase; healing when necrotic tissue was mostly replaced by connective tissue with macrophages and fibroblasts; old when dense avascular and hypocellular fibrous tissue was detected. Substitutive myocardial fibrosis was defined as microfocal (≤ 5%) or extensive (> 5%) and subdivided into massive or focal-confluent, interstitial or perivascular and intermyocellular.

A lymphocytic infiltrate was formed by ten or more elements. According to location they were defined as: a) intramyocardial subdivided in intermyocellular (when found in the interstitium between myocells and distinguished in associated or not to myocell necrosis) and perivascular (when observed in interfascicular-perivascular spaces). A coronary artery stenosis was functional when lumen-diameter reduction, measured on the histological slide, was ≥ 70% of the normal diameter of the coronary artery or main branch.

Death was categorised as instantaneous when, according to witnesses, it occurred in less than 5 min and rapid within 1–12 h. The survival period is the interval between the onset of the terminal episode and death.

### Statistics

Data are expressed as mean values ± one standard deviation. Student's *t*-test for paired or unpaired date or nonparametric Mann-Whitney or Wilcoxon tests for skewed variables or one-way analysis of variance and post hoc Scheffe's test for continuous variables and $\chi^2$ test for discrete variables were used to assess statistically significant differences. Linear regression analysis was used to determine the presence of correlation between continuous variables. A probability $p$ measured value < 0.05 was considered significant.

## Results

The 26 chronic cocaine abusers consisted of 20 males and 6 females with a mean age of 35 ± 6 years (range 20–45 years) and the drug addiction lasted from 1–10 years. All subjects died from cocaine intoxication and the terminal episode lasted more than 8 h in 14 of the individuals. The cocaine blood level at the time of death varied from trace levels to 8.0 mg/l (metabolites blood levels ranged from trace to 18 mg/l). In 10 cases cocaine was associated only with ethyl alcohol. The levels of alcohol found in the blood ranged from trace to 0.8 g/l. In no case was the concentration of other drugs (benzodiazepins) found in the blood or urine at the time of death considered to be responsible for death. In the selected cases resuscitation did not take place. In the 45 head trauma subjects 37 were men and 8 women with a mean age of 42 ± 17 years (range 15–75 years), while in the AIDS subjects the figures were 33 and 5 with a mean age of 31 ± 10 years (range 21–63 years). The heart weight was similar in all three groups. In Table 1 the main parameters of the three groups are reported.

### Acute myocardial necrosis

The types of myocardial necrosis found in cocaine subjects were coagulative myocytolysis and reflow necrosis. No histological signs of infarct necrosis were detected. Coagulative myocytolysis was present in 11 (42%) of the 26 chronic cocaine abusers, with a number of foci and necrotic myocells × 100 mm$^2$ of 4 ± 4 (range 0.3–14) and 11 ± 14 (0.3–36) respectively (Table 2). In most of the cases the lesion was early (anomalous cross bands). The alveolar/healing phase was never seen. A microfocal reflow necrosis was observed in the anterior papillary muscle two (8%) of these cases.

In head trauma controls the acute myocardial necrosis found was coagulative myocytolysis with a 4% frequency in the 26 subjects who died instantaneously and a 42% in

**Table 1** Main parameters of chronic cocaine abusers and controls

| Source | No cases | Gender | | Age (years) | | Heart weight | | Cocaine (or metabolites) blood level* (mg/L) | Alcohol blood level* (g/L) | Survival period last episode |
|---|---|---|---|---|---|---|---|---|---|---|
| | | M | W | Mean | Range | Mean | Range | | | |
| Chronic cocaine abusers | 26 | 20 | 6 | 35 ± 6 | 20–45 | 351 ± 32 | 295–390 | trace –18.0 | trace –0.8 | > 5–12 h |
| AIDS | 38 | 33 | 5 | 31 ± 10 | 21–63 | 368 ± 67 | 250–500 | 0.0 | 0.0 | > 5 days |
| Head trauma controls | 45 | 37 | 8 | 42 ± 17 | 15–75 | 364 ± 47 | 280–500 | 0.0 | 0.0 | < 5 min–12 h |
| Instantaneous death | 26 | 20 | 6 | 42 ± 18 | 17–75 | 362 ± 44 | 280–470 | 0.0 | trace –1.9 | < 5 min |
| Rapid death | 19 | 17 | 2 | 42 ± 17 | 15–69 | 367 ± 53 | 290–500 | 0.0 | 0.0 | 1–12 h |

* post-mortem

**Table 2** Quantification of coagulative myocytolysis and intramyocardial lymphocytic infiltrates

| Source | No cases | Coagulative myocytolysis | | | | | Lymphocytic infiltrates | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | + | No foci* | Range | No myocells* | Range | + | Intermyocel. | | Perivasc. | No foci* | Range |
| | | | | | | | | – Mn | + Mn | | | |
| Chronic cocaine abusers | 26 | 11 | 4 ± 4 | 0.3 –14 | 11 ± 14 | 0.3 –36 | 5 | 3 | – | 3 | 0.8 ± 5 | 0.04– 1 |
| AIDS | 38 | 25 | 4 ± 11 | 0.03–55 | 13 ± 27 | 0.03–98 | 19 | 16 | 9 | 5 | 1.5 ± 3 | 0.03–11 |
| Head trauma controls | 45 | 9 | 10 ± 18 | 0.3 –46 | 23 ± 31 | 0.3 –90 | 16 | 11 | – | 14 | 5 ± 9 | 0.3 –34 |
| Instantaneous death | 26 | 1 | 0.5 | | 35 | | 8 | 5 | – | 7 | 1 ± 0.5 | 0.5 – 2 |
| Rapid death | 19 | 8 | 12 ± 18 | 0.3 –46 | 21 ± 33 | 0.3 –90 | 8 | 6 | – | 7 | 9 ± 13 | 0.3 –34 |

*× 100 $mm^2$; + = present; MN = myocell necrosis

19 who died rapidly. In the latter subgroup two hearts presented an early alveolar pattern of this form of necrosis. The number of foci and myocells were 0.5 and 35 and 12 ± 18 (0.3–46) and 21 ± 33 (0.3–90) respectively. In the 38 AIDS patients four cases with normal coronary arteries had a microfocal infarct in a papillary muscle, 25 (65%) had coagulative myocytolysis with the number of foci of 4 ± 11 (0.03–55) and myocells of 13 ± 27 (0.03–98). The lesion was early in 19 and alveolar in 6 patients.

### Myocardial fibrosis

Chronic cocaine abusers showed subendocardial microfocal (3 cases) or extensive (≤ 30% in 3 cases) myocardial fibrosis in six while two head trauma controls had extensive (≤ 30%) and four microfocal subendocardial myocardial fibrosis. Microfocal myocardial fibrosis was found in 4 AIDS patients.

### Inflammatory infiltrates

Lymphocytic infiltrates were seen in 19% of chronic cocaine abusers and 35% of normal subjects with head trauma and in 50% of AIDS patients. In 24% of the latter the infiltrates were associated with myocell necrosis. The number of lymphocytic foci × 100 $mm^2$ was 0.8 ± 0.5 (0.04–1) for chronic cocaine abusers, 1.5 ± 3 (0.03–11) for AIDS patients 1 ± 0.5, (0.5–2) for head trauma subjects who died instantaneously and 9 ± 13 (0.3–34) for head trauma in the rapid death group. No other type of infiltrates (eosinophils, etc.) or changes were observed. In particular no lesions of the intramyocardial vessels (platelet aggregates, thrombus, intimal thickening, etc) were seen.

## Discussion

In the literature many reports postulated a relationship between cocaine abuse and cardiac disorders, particularly of ischemic nature. However, a literature review of both autopsy [6–19] and clinical [20–47] cases related to cocaine intoxication show an absence of postmortem documentation of an ischemic pathogenesis. The few cases defined as myocardial infarction had contraction band necrosis. Our discussion is based on findings observed in subjects selected according to the following criteria: chronic abuse of cocaine and cocaine-related death in the absence of median-severe coronary atherosclerosis (≤ 50% of lumen-diameter reduction) and any potentially fatal disease.

### Type and extent of acute myocardial necrosis

The unique form of acute myocardial necrosis found in cocaine subjects was coagulative myocytolysis. In no one instance were we able to observe infarct necrosis, particularly in chronic abusers with survival longer than 8 h after the last episode. Such a longer survival should be sufficient for a histological evidence of this necrosis. Our findings apparently contrast with many reports of myocardial infarct associated with cocaine. The precise histology of the infarct is often not reported or referred to as “myocardial necrosis” or “microfocal contraction band necrosis”, in different histological stages, typical for coagulative myocytolysis. It must be stressed that infarct necrosis has an opposite morpho-functional pattern with different biochemical impairment and pathogenic mechanisms in respect of coagulative myocytolysis [2–3].

Coagulative myocytolysis is observed in many human and experimental conditions, including ischemic heart disease [2]. However, several facts support the view that coagulative myocytolysis is due to catecholamine cardiotoxicity which can be reproduced experimentally [4, 5]. This toxicity seems to be due to an excess of intramyocellular $Ca^{++}$ cell influx rather than coronary spasm demonstrated only in one out of 46 cases by cineangiography [39] and/or increased oxygen demand of myocells, or reflow. In the latter an association of contraction bands and massive interstitial hemorrhage is present [2]; a finding never observed in our material.

In cocaine addicts the frequency and extent of coagulative myocytolysis were similar to AIDS patients and lower than head trauma normal controls who had a longer (1–12 h) survival. Despite our limitation in defining “instantaneous” a demise often reported by non-expert wit-

nesses, one notes the very low frequency and extent of coagulative myocytolysis in head trauma controls where death occurred in very short time in contrast with those with longer survival times. This finding suggests that coagulative myocytolytic changes may be related to the type and length of survival particularly in subjects predisposed to cardiac adrenergic response. The omission of the variable "survival" could explain divergencies found in literature on the frequency of this lesion. In other words, any attempt to evaluate its meaning requires a quantitative study, the recognition of older stages, the determination of survival time and the exclusion of reanimative procedures.

The other main point to stress is the minimal amount of tissue loss due to coagulative myocytolysis seen in cocaine and control groups. This minimal loss of tissue cannot, per se, jeopardize myocardial function and cause death.

### Recent and old myocardial damage

More advanced stages of coagulative myocytolysis (alveolar or healing patterns) and old myocardial fibrosis were practically absent or minimal in cocaine subjects and controls. This indicates that a recurrent myotoxicity of cocaine can not be demonstrated by histology.

### "Inflammatory" infiltrates

No histological indication of myocarditis was seen in cocaine addicts. Lymphocytic infiltrates of unknown nature, were observed in 19% of cocaine addicts, in 35% of head trauma controls and 50% of AIDS patients. An association with myocardial necrosis was only detected in the latter group [1]. However, the number of lymphocytic foci was low in all cases. The number of lymphocytic infiltrates was higher in head trauma controls with longer survival times. Activation of dendritic-lymphocytes normally present in the myocardium [48] may occur in the latter period. To explain divergencies in the literature on the presence or absence of myocarditis in cocaine abusers and whether myocarditis is eosinophilic or not, one should remember that drug addicts are a very heterogeneous population, with many other concurrent factors (infectious disease, etc).

The criteria of selection of our material do not permit any contribution to the possible role of cocaine in anticipating atherosclerotic processes. In 46% of 13 young (mean age 32 years) subjects with cocaine-related death a severe (≥ 75%) coronary atherosclerosis was seen in contrast to 2 (22%) out of 9 individuals who died from other causes [14]. Mast cells have been proposed as a factor for accelerated atherosclerosis, thrombosis and premature sudden death in long term cocaine abusers [49]. It is known that cocaine potentiates catecholamine action by inhibition of the presynaptic uptake carrier [50]. In some cases or conditions an enhanced catecholamine effect may lead to severe and diffuse coagulative myocytolysis and fibrin-platelet thrombi related to catecholamines [2] and/or cocaine [50] procoagulant effect. Coagulative myocytolysis, even if confined to one or few myocells, can be interpreted as a histological sign of adrenergic overdrive. It remains to be established if due to unspecific agonal stimuli or drug action.

Keeping in mind that the incidence of acute myocardial infarction in cocaine addicts with chest pain is low [51], our conclusions are:

1. Contraction band necrosis and/or lymphocytic infiltrate are not specific for cocaine-related death. Quantification of these parameters showed lower values compared to normal subjects who died for head trauma after a terminal episode longer than 1 h.

2. Adrenergic overactivity in chronic cocaine abuse does not induce significant myocell necrosis, as shown by the absence of myocardial fibrosis and late phase of coagulative myocytolysis.

3. One cannot exclude that in a few subjects, for an unknown cause, an adrenergic crisis with severe coagulative myocytolysis (not be confused with myocardial infarction) and fibrin-platelet thrombi leading to sudden death or an infarct-like clinical pattern associated with malignant arrhythmia (ventricular fibrillation) may occur.

From the diagnostic standpoint, the proposed algorhythm for cocaine-related sudden death [52–53], should include a quantification of coagulative myocytolysis [54].

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