



Silent myocardial damage in cocaine addicts

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ABSTRACT

Background Cocaine addiction is associated with either ischaemic or non-ischaemic cardiac complications. The prevalence of myocardial damage in asymptomatic addicts has never been evaluated by cardiovascular magnetic resonance (CMR), which allows non-invasive detection of myocardial oedema and fibrosis.

Objective To prospectively evaluate the prevalence of myocardial damage in cocaine addicts with no history of cardiac disease by CMR.

Methods Thirty consecutive subjects (25 men, mean age 39 ± 7 years), with no history of cardiac symptoms/disease were evaluated 48 h after the withdrawal of cocaine by a comprehensive humoral, clinical and instrumental assessment, including B-type natriuretic peptide and troponin I assay, echocardiography, exercise stress test and 24 h ECG recording, as well as CMR examination. The CMR study was performed using a 1.5 Tesla scanner. Myocardial oedema was evaluated by a T2-weighted STIR sequence and fibrosis using the late gadolinium enhancement technique.

Results Biohumoral markers of cardiac involvement were negative in all subjects except one. Fifteen subjects had subtle abnormalities at resting ECG, while exercise stress testing and Holter studies were negative for ischaemic or arrhythmic events. Echocardiography provided evidence of wall motion abnormalities in 12 subjects. At CMR evaluation, myocardial involvement was detected in 25 subjects (83%), oedema in 14 (47%) and fibrosis in 22 (73%). Eleven subjects (37%) showed both myocardial oedema and fibrosis with similar localisations in nine. Seven subjects had ischaemic patterns of fibrosis and 15 had non-ischaemic patterns of fibrosis.

Conclusions A high prevalence of cardiac damage in asymptomatic cocaine addicts can be found by CMR examination.

Cocaine is the most commonly used illicit drug in Western countries with 6.4 million people aged between the ages of 15 and 64 using cocaine in the USA, giving an annual prevalence of 2.6%.¹ Cocaine may induce non-ischaemic myocardial damage by increasing the sympathetic drive causing contraction band necrosis, myocyte necrosis and apoptosis in the experimental setting,^{2,3} whereas myocarditis has been reported in 20% of addicts in autopsy studies.⁴ Overt myocardial infarction occurs in 0.7–6% of subjects presenting with chest pain associated with cocaine use.⁵ Moreover, 25% of non-fatal myocardial infarctions in subjects aged <45 years have been attributed to cocaine abuse⁶ and 3.1% of sudden deaths were cocaine related.^{7,8} Cardiac toxicity is further increased when use of cocaine is combined with ethanol and/or opioids.⁹

In cocaine addicts enrolled in treatment programmes the mortality rate was significantly

higher than in the general population, with cardiovascular deaths accounting for the excess mortality.¹⁰

Cardiac magnetic resonance (CMR) is considered the 'gold standard' imaging technique for evaluation of cardiac function and detection and quantification of the extent of myocardial damage, including ischaemic fibrosis, non-ischaemic fibrosis and oedema.^{11,12}

Our aim was to evaluate the prevalence, characteristics and clinical correlates of cardiac toxicity in asymptomatic cocaine addicts with no history of cardiac symptoms/disease by a comprehensive evaluation including CMR. As far as we know, these parameters have never before been prospectively evaluated together.

METHODS

Population

We screened 40 consecutive cocaine addicts (32 men, mean age 39 ± 6 years), who entered a residential rehabilitation programme (see online supplementary data). All had a clinical psychiatric diagnosis of cocaine addiction, as inclusion criterion, and these diagnoses were supported by findings from urine immunoassays for cocaine and its major metabolites. Exclusion criteria were a previous history and/or current symptoms of coronary artery, valvular, pericardial or myocardial disease of any aetiology and/or inability to undergo CMR examination. Subjects were evaluated by a comprehensive cardiological diagnostic investigation, beginning 48 h after drug withdrawal.

Of the 40 subjects, 10 refused consent or did not complete the CMR evaluation. A total of 30 subjects (25 men, mean age 39 ± 7 years) were finally enrolled and underwent a thorough evaluation. Cardiac evaluation included history, physical examination, resting 12-lead electrocardiogram, two-dimensional Doppler echocardiography and stress test by exercise on a bicycle ergometer. A standardised, stepwise (with increments of 25 W every 2 min) and symptom-limited bicycle exercise test was performed in all subjects to the end points as defined in the exercise testing guidelines.¹³ A 12-lead ECG was continuously recorded during exercise and recovery. Blood pressure was recorded every minute during exercise and recovery. ST-segment deviation was visually controlled and interpreted by an experienced cardiologist according to the criteria outlined by current guidelines. Twenty-four-hour ECG Holter monitoring was recorded for conventional and time-domain analysis of heart rate variability: SD of RR intervals, SD of the average normal to normal QRS (NN) intervals calculated over periods of 5 min (SDANN); the number of interval differences of successive NN intervals >50 ms divided by the total number of

NN intervals (pNN50); the square root of the mean squared differences of successive NN intervals (RMSSD).¹⁴

A high-sensitivity troponin I assay was evaluated by a chemiluminescent immunoassay (ADVIA cTnI-Ultra method, Siemens Medical Solutions, Erlangen, Germany). Brain natriuretic peptide (BNP), the N-terminal fragment of pro-BNP (NT-proBNP) and plasma catecholamines were evaluated as previously described.¹⁵

Urine assays of cocaine metabolites (benzoylecgonine and ecgonine methyl ester) were performed by the enzyme multiplied immunoassay technique (EMIT; Syva, San Jose, California, USA) 14 days before entry into the rehabilitation programme, the day after drug withdrawal and the day of the CMR examination.

CMR

A CMR examination was performed using a dedicated 1.5 T scanner (Signa Hdx; General Electric Healthcare, Milwaukee, Wisconsin) with an eight-channel cardiac phased array coil.

Evaluation of ventricular functional parameters was performed by the acquisition of a set of ventricular short-axis cine images from the mitral plane valve to the left ventricular apex using a steady-state free precession (FIESTA) pulse sequence (30 phases, slice thickness 8 mm, no gap, eight views per segment, NEX 1, FOV 40 cm, phase FOV 1, matrix 224×224, reconstruction matrix 256×256, 45° flip angle, TR/TE=3.5/1.5 and a bandwidth of 125 KHz).¹⁶

Myocardial oedema was evaluated using a T2-weighted short-inversion time IR FSE (STIR) pulse sequence acquired in the same views as above (FOV 40 cm, TR as two RR intervals, TE 70 ms, TI 150 ms, matrix 256×256, reconstruction matrix 512×512, slice thickness 8 mm).¹⁷ Myocardial oedema was defined as an area of hyperintense myocardium with a signal intensity twofold higher than the mean signal intensity of adjacent skeletal muscles.^{18–19} The presence of myocardial oedema was also confirmed by acquisition of T2-weighted STIR images using a body coil with the same parameters.

Myocardial fibrosis was evaluated by the late gadolinium enhancement (LGE) technique.²⁰ Briefly, LGE images were acquired after administration of Gd-DTPA (Magnevist, Schering-AG, at a dosage of 0.2 mmol/kg) in short-axis and long-axis views using a T1-weighted IR GRE pulse sequence (FOV 40 cm, slice thickness 8 mm, no gap, TR 4.6 ms, TE 1.3, flip angle 20, matrix 224×192, reconstruction matrix 256×256, NEX 1, inversion time was chosen to null signal of normal myocardium). Quantification of the extent of fibrosis at LGE imaging was performed as previously described,²¹ and three patterns of presentation were defined: (1) absence of fibrosis when myocardial enhancement was not detected; (2) ischaemic pattern; (3) non-ischaemic pattern. The ischaemic pattern was defined by confluent enhancement involving the subendocardial layer with/without transmural extension localised in a definite coronary artery vascularisation territory. A non-ischaemic pattern was defined by a non-confluent or diffuse enhancement, usually located in the epicardium or in the middle layer and not confined to a vascularisation territory.²²

Coronary artery evaluation

Study protocol included the evaluation of coronary artery disease in patients with a positive exercise stress test or with a negative exercise stress test but with an ischaemic pattern of LGE on CMR. Coronary artery evaluation was performed by coronary angiography in patients with a positive exercise stress test or by coronary CT angiography in patients with negative exercise stress test and an ischaemic pattern of LGE on CMR. Coronary artery disease was defined for coronary lumen narrowing >50%.

Statistical analysis

Continuous values are expressed as the mean±SD for normally distributed variables and as median and 25th–75th centiles for variables with non-normal distributions. Variables with skewed distributions were logarithmically transformed before further analysis. Categorical variables were compared by Pearson's χ^2 test or Fisher's exact test, when appropriate. One-way analysis of variance or Bonferroni's post hoc test, when appropriate, was used to compare quantitative variables across groups. A p value <0.05 was considered statistically significant.

RESULTS

Population

Of the 30 cocaine addicts studied, 16 (53%) were polydrug addicts (nine cocaine and opioids, six cocaine and ethanol and one cocaine, opioids and ethanol). The mean drug abuse duration was 12±6 years (range 3–24), and average self-reported street cocaine daily consumption was 5.4±7.1 g. Ten subjects reported intravenous use of cocaine, 18 by inhalation (sniffing) and two by smoking (crack).

At enrolment 13 subjects (43%) had positive urinary assays for cocaine and metabolites, though only eight (27%) subjects reported recent drug consumption (table 1). Six subjects were

Table 1 Population characteristics

Variables	Value
General characteristics	
Number	30
Age (years)	39±7
Male, n (%)	25 (83)
Single-drug abusers (cocaine), n (%)	14 (47)
Polydrug abusers, n (%)	16 (53)
Positive cocaine and metabolites assay (at enrolment), n (%)	13 (43)
Last time of consumption (days before CMR)	70±109
Consumption during past 2 weeks, n (%)	8 (27)
Duration of addiction (years)	12±6
Reported dose (g/dose)	7.4±7.0
Echocardiography	
Ejection fraction (%)	64±4
Septal end-diastolic thickness (mm)	9±2
E wave (cm/s)	73±14
A wave (cm/s)	50±14
E/A	1.54±0.39
Deceleration time (ms)	204±24
Right ventricular systolic pressure (mm Hg)	26±4
CMR	
LVEDVi (ml/m ²)	80±15
LVESVi (ml/m ²)	27±6
LV mass index (g/m ²)	70±11
LVEF (%)	66±5
WMSI	1.02±0.03
Biomarkers	
Epinephrine (pg/ml)	32±34
Norepinephrine (pg/ml)	336±172
Dopamine (pg/ml)	56±68
NT-proBNP (ng/l)	40±65
hs-Troponin I (ng/ml), median (25th–75th)	0.007 (0.006–0.0195)

Values are expressed as mean±SD for continuous normally distributed variables and as median (25th to 75th centile) for continuous non-normally distributed variables, unless otherwise stated.

CMR, cardiovascular magnetic resonance; hs, high sensitivity; LV, left ventricular; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; NT-proBNP, N-terminal pro-brain natriuretic peptide; WMSI, wall motion score index.

positive for infection by the hepatitis C virus and one of them was also positive for human immunodeficiency viral infection.

Cardiovascular evaluation

All subjects were in sinus rhythm with no Q waves on standard ECG. A normal ECG was found in 14 subjects, while 16 subjects had subtle ECG abnormalities (eight had a lack of normal R-wave progression in precordial leads, three had 0.05 mV ST-segment elevation in the inferior leads; three had T-wave abnormalities, one had an R/S amplitude ratio >1 in V2).

Upon 24 h Holter monitoring, the average heart rate was 76 ± 10 bpm (maximal heart rate 125 ± 12 , minimal 49 ± 8 bpm), with analysis of heart rate variability showing average values within the normal range (SD of the RR interval 124 ± 40 ms, SDANN 112 ± 39 ms, RMSSD 32 ± 15 ms, pNN50 $7 \pm 7\%$). No episodes of significant bradyarrhythmias, supra-, ventricular tachyarrhythmias or significant transient ST-segment changes were recorded. The average number of premature ventricular beats was 277 ± 1474 and one subject only showed a Lown $>II$ classification (IVb). At the exercise stress test, the average exercise capacity was 148 ± 40 W (range 75–225 W) and the average double product was $24\,660 \pm 4200$. In 20 subjects heart rate was $>85\%$ of the predicted maximal heart rate. Test was negative for angina, ischaemia and arrhythmias in all the subjects.

By echocardiography, global LV function was normal (ejection fraction $>55\%$) in all subjects, whereas regional wall motion abnormalities were found in 12. Three subjects showed a mitral

inflow pattern of impaired relaxation. One subject had mild septal hypertrophy. Significant valvular disease was not detected in any subject. Estimated right ventricular systolic pressure was within the normal range in all subjects.

The average values of humoral biomarkers are reported in table 1. High-sensitivity troponin I was within the reference range in all subjects except one (0.1 ng/ml, reference value <0.07).

CMR results

CMR confirmed the normal left ventricular ejection fraction in all subjects, while identifying regional left ventricular hypokinesia in 12 (40%), with an 80% concordance with echocardiographic findings. Slight dilatation of the left or right ventricle was found in one and three subjects, respectively and left ventricular hypertrophy was found in two subjects.

As shown in table 2, oedema of the left ventricle was found in 14 subjects (47%) and fibrosis was found in 22 (73%), including seven with ischaemic patterns (figure 1) and 15 with non-ischaemic patterns (eight in the mid-wall, four in the subepicardial layer and three at the ventricular junctions; diffuse fibrosis in four, focal in 12 subjects; an example is shown in figures 2 and 3). No specific sites of either oedema or fibrosis were identified. The average extent of fibrosis was $2.3 \pm 3.2\%$ of left ventricular mass (range 0.4–16%). Eleven subjects (37%) showed both myocardial oedema and fibrosis and in nine of these patients, oedema and fibrosis involved the same myocardial segments.

Table 2 Cardiovascular magnetic resonance findings

Patient	Age (years)	Sex	Drug	Oedema	Fibrosis	Site of oedema	Site of fibrosis	Pattern of fibrosis	Site concordance
1	35	M	Cocaine	Yes	Yes	Inferior, inferoseptal, inferolateral	Inferoseptal	Non-ischaemic	Yes
2	46	M	Cocaine	Yes	Yes	Inferior	Inferior, inferoseptal	Non-ischaemic	Yes
3	34	M	Cocaine	No	No	—	—	—	—
4	37	M	Cocaine	No	Yes	—	Inferolateral	Ischaemic	—
5	52	M	Cocaine	No	Yes	—	Anteroseptal, anterolateral	Ischaemic	—
6	39	M	Cocaine-opioids	No	Yes	—	Inferoseptal	Non-ischaemic	—
7	34	M	Cocaine-opioids	No	Yes	—	Inferoseptal	Non-ischaemic	—
8	51	M	Cocaine	No	Yes	—	Inferoseptal	Non-ischaemic	—
9	36	M	Cocaine	No	No	—	—	—	—
10	32	M	Cocaine	Yes	Yes	Inferolateral	Inferolateral	Non-ischaemic	Yes
11	43	F	Cocaine	No	No	—	—	—	—
12	45	M	Coca-opioids	No	No	—	—	—	—
13	44	M	Coca-opioids	Yes	No	Inferior, inferoseptal, inferolateral	—	—	—
14	24	F	Coca-opioids	Yes	Yes	Anterior, anteroseptal	Anterior	Non-ischaemic	Yes
15	39	F	Coca-opioids	Yes	No	Inferior	—	—	—
16	32	M	Coca-ethanol	No	No	—	—	—	—
17	36	M	Cocaine	Yes	No	Anterior, anteroseptal	—	—	—
18	44	M	Coca-ethanol	Yes	Yes	Inferoseptal	Inferoseptal, Anteroseptal	Non-ischaemic	Yes
19	36	M	Coca-ethanol	Yes	Yes	Anterior	Anterior	Non-ischaemic	Yes
20	47	M	Coca-opioids	No	Yes	—	Anterior, anteroseptal	Ischaemic	—
21	37	M	Coca-ethanol	No	Yes	—	Inferolateral, inferior	Non-ischaemic	—
22	46	M	Cocaine	No	Yes	—	Inferior, inferoseptal	Ischaemic	—
23	32	M	Coca-ethanol	Yes	Yes	Septal	septal	Non-ischaemic	Yes
24	33	F	Cocaine	No	Yes	—	Anteroseptal, anterolateral	Ischaemic	—
25	42	M	Coca-opioids	Yes	Yes	Septal	Septal	Non-ischaemic	Yes
26	52	M	Coca-opioids	No	Yes	—	Septal	Non-ischaemic	—
27	35	M	Coca-ethanol	No	Yes	—	septal	Non-ischaemic	—
28	39	M	Cocaine	Yes	Yes	Anterior	Inferolateral	Ischaemic	No
29	31	F	Cocaine	Yes	Yes	Anteroseptal	Inferior	Ischaemic	No
30	43	M	Coca-ethanol-opioids	Yes	Yes	Anterolateral	Anterior, anterolateral, anteroseptal	Non-ischaemic	Yes

Site concordance: patients with myocardial oedema and fibrosis within the same myocardial region.

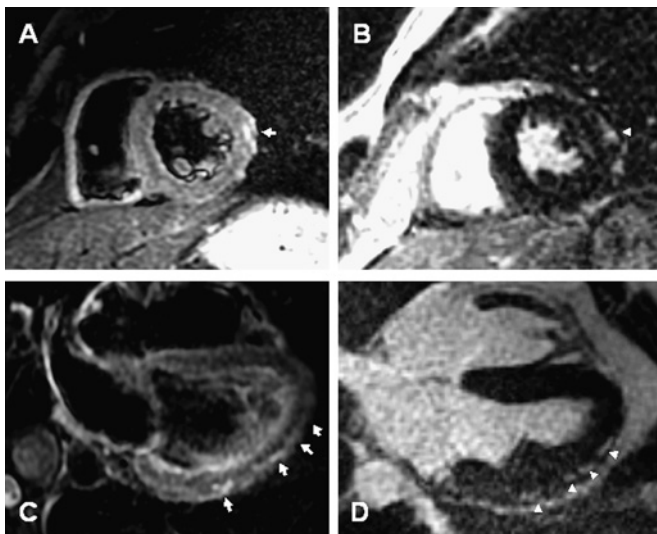


Figure 1 Non-ischæmic patterns of fibrosis and myocardial oedema in a cocaine addict. Areas of hyperintense myocardium corresponding to myocardial oedema are indicated in the epicardial layer of the lateral wall (arrows) on the short axis (A) and the horizontal long axis (C). T2-weighted short tau-inversion recovery (STIR) image. In panels B and D, late gadolinium enhancement (LGE) images acquired, respectively, in the short- and long-axis planes show myocardial enhancement in the epicardial layer (arrowheads), corresponding to myocardial fibrosis with a non-ischæmic pattern of presentation.

Among the 22 subjects with signs of fibrosis in LGE images, 10 (45%) were single-drug addicts and 12 (55%) were polydrug addicts. Polydrug addicts had a higher prevalence of non-ischæmic patterns (one ischæmic vs 11 non-ischæmic, $p < 0.01$). All six subjects with combined addictions of cocaine and ethanol had positive LGE images with non-ischæmic patterns.

No difference was found in the LGE patterns (six ischæmic vs four non-ischæmic) of single-drug addicts.

Clinical correlates of myocardial oedema

The relationship between clinical variables and myocardial oedema is summarised in table 3.

Signs of myocardial oedema by CMR were associated with greater self-reported consumption of cocaine. Out of 14 subjects with oedema, 12 (86%) had one or more positive urinary assay for cocaine metabolites. No significant difference was found in the self-reported temporal interval between CMR and last

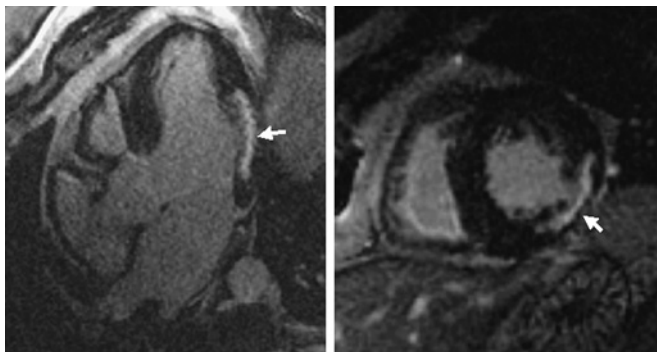


Figure 2 In the left and right panels, two late gadolinium enhancement (LGE) images are shown in long- and short-axis views, respectively. Both images show a confluent, transmural fibrosis (ischæmic pattern) (arrows).

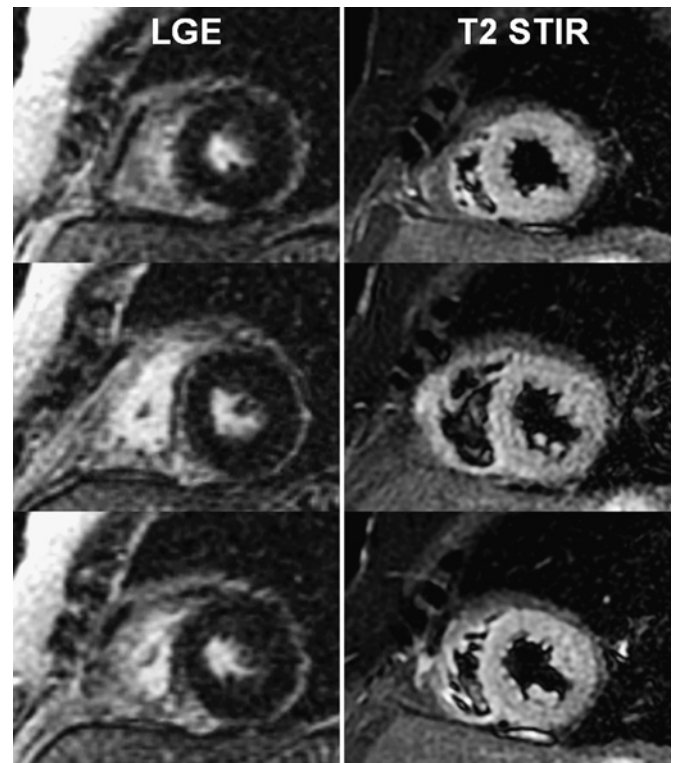


Figure 3 Example of a cocaine addict with fibrosis in the intramural layer of the inferoseptal and anteroseptal walls (short-axis late gadolinium enhancement (LGE) images in left panels) but without myocardial oedema (short-axis T2-weighted short tau-inversion recovery (STIR) images in right panels).

consumption between subjects with and those without myocardial oedema (68 ± 99 vs 72 ± 129 days, $p = 0.93$).

Six subjects showed slight abnormalities at the resting ECG. A lack of normal R-wave amplitude progression of R in precordial leads in four subjects was associated with anterior or anteroseptal oedema, whereas slight ($=0.05$ mV) ST-segment elevation on the inferior leads was found in one patient with inferolateral oedema and fibrosis (figure 1) and we observed an R/S amplitude ratio > 1 in V2 in one subject with septal oedema. No significant difference was found during stress ECG test (data not presented).

Detection of oedema was associated with depressed heart rate variability (lower SD of RR), with a higher mean heart rate and lower SDANN (table 3). Upon Doppler study of transmitral flow, the E wave was significantly higher in subjects with myocardial oedema than in those without (table 3).

Subjects with myocardial oedema showed a trend towards higher values of high sensitivity troponin I than those without oedema ($p = 0.07$).

At CMR, oedema was associated with a significantly higher ejection fraction ($p = 0.02$) and a lower end-systolic volume ($p = 0.04$) (table 3).

Clinical correlates of myocardial fibrosis

The relationships between clinical variables and myocardial fibrosis are summarised in table 3. Evidence of fibrosis at CMR was not associated with self-reported levels of consumption.

Fourteen (63%) subjects showed abnormalities at the resting ECG. A lack of normal R-wave amplitude progression in precordial leads (seven subjects) and T wave abnormalities (two subjects) were associated with evidence of fibrosis in remote

Table 3 Clinical variable, myocardial oedema and late gadolinium enhancement

Variables	Myocardial oedema			Myocardial fibrosis		
	Yes	No	p Value	Yes	No	p Value
Number	14	16		22	8	
Age (years)	41±7	37±6	0.17	39±8	39±5	0.78
Male (n)	11/25	14/25	0.5	19/25	6/25	0.9
Polydrug abusers (n)	8/16	8/16	0.69	12/16	4/16	0.69
Duration of addiction (years)	13±6	11±6	0.36	12±5	13±8	0.74
Reported dose (g)	7.4±7	3.3±1.7	0.04	5.6±6	4.3±2	0.56
Positive urinary assay (n)	12	1	0.001	7	6	0.66
HCV/HIV infections (n)	3	3	0.86	2	4	0.60
Biomarkers						
Epinephrine (pg/ml)	21±21	30±30	0.36	27±25	45±56	0.27
Norepinephrine (pg/ml)	375±222	301±140	0.59	337±197	307±63	0.70
Dopamine (pg/ml)	67±79	34±47	0.34	52±60	47±88	0.88
NT-proBNP (ng/l)	27±26	56±87	0.36	44±73	28±23	0.62
hs-troponin I (ng/ml)	0.013	0.006	0.07	0.006	0.008	0.7
Median (25th–75th)	(0.006–0.05)	(0.006–0.009)		(0.006–0.031)	(0.006–0.024)	
Transmitral flow (pulse wave Doppler):						
E wave (cm/s)	79±13	61±11	0.01	75±15	70±15	0.63
A wave (cm/s)	51±14	47±15	0.5	51±15	48±12	0.72
E/A	1.6±0.4	1.4±0.4	0.35	1.56±0.45	1.48±0.14	0.75
Deceleration time (ms)	205±26	199±16	0.67	211±20	172±12	0.02
RV systolic pressure (mm Hg)	26±4	26±2	0.27	24±5	28±3	0.27
24-hour Holter ECG						
Heart rate (bpm)	79±10	72±8	0.04	75±10	74±4	0.82
SDNN (ms)	112±35	141±37	0.04	130±42	118±20	0.55
SDANN (ms)	100±34	127±36	0.06	117±41	105±22	0.53
pNN50 (%)	6.9±7	9±8	0.34	9±8	32±2	0.52
RMSSD (ms)	30±15	36±14	0.35	35±16	21±9	0.22
CMR						
LVEDVi (ml/m ²)	80±15	81±13	0.83	81±15	81±10	0.9
LVESVi (ml/m ²)	27±6	33±9	0.04	30±8	30±10	0.95
LV mass index (g/m ²)	70±11	70±12	0.95	70±11	70±12	0.95
LVEF (%)	66±5	59±8	0.02	62±7	63±10	0.85
WMSI	1.02±0.03	1.08±0.13	0.14	1.05±0.07	1.07±0.17	0.53

Values are expressed as mean±SD for continuous normally distributed variables and as median (25th to 75th percentile) for continuous non-normally distributed variables, unless otherwise stated.

CMR, cardiovascular magnetic resonance; hs-troponin I, high sensitivity troponin I; LV, left ventricular; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; pNN50, number of interval differences of successive NN intervals >50 ms divided by the total number of NN intervals; RMSSD, square root of the mean squared differences of successive NN intervals; RV, right ventricular; SDANN, SD of the average NN interval calculated over periods of 5 min; SDNN, SD of beat-to-beat NN interval, WMSI, wall motion score index.

regions, whereas slight (≈ 0.05 mV) ST-segment elevation on the inferior leads in three subjects and an R/S amplitude ratio >1 in V2 in one subject, were associated with the concordant site of fibrosis (inferolateral or inferoseptal wall).

The transmitral flow of subjects with fibrosis showed higher deceleration times than those of subjects without fibrosis.

One subject with a positive urinary assay for cocaine showed a slight increase in ultrasensitive troponin I (0.1 ng/ml, reference value <0.07) and evidence of both oedema and LGE on CMR.

Coronary CT angiography was performed in seven patients with ischaemic pattern of LGE on CMR. Coronary artery disease was detected in only one patient (male, aged 52 years, with no cardiovascular risk factors, but history of untreated arterial hypertension), by CT and confirmed by coronary angiography.

DISCUSSION

This study indicates a high prevalence (83%) of myocardial structural damage in asymptomatic cocaine addicts who were studied with CMR ≥ 48 h after drug withdrawal. While myocardial oedema and fibrosis were previously reported in a cocaine addict presenting with chest pain at an emergency room,²³ this is the first prospective study examining the

potential for chronic silent cardiac involvement using CMR, which allows the in vivo identification of myocardial oedema by T2-weighted pulse sequences¹⁷ as well as detection of myocardial fibrosis.²⁴

Fibrosis, which was found in 73% of the subjects, is probably a consequence of silent myocardial damage occurring any time during chronic exposure to the drug, while focal oedema, which was seen in 47% of the subjects, is secondary to a relatively recent exposure. Cardiac involvement recognises heterogeneous focal distribution throughout all left ventricle segments.

Worth noting is that the presence of myocardial oedema was associated with greater reported doses of cocaine and frequent (86%) positive urinary assays for cocaine and metabolites in the days preceding CMR, thus suggesting a toxic, dose-related effect.

Myocardial oedema is potentially reversible. It can be secondary to a prolonged ischaemic event (usually undetectable after 1 month)²⁵ or to a toxic or inflammatory myocardial injury (CMR evidence persisting for up to 6 months).¹⁷

In this series, the presence of oedema was associated with lower left ventricular end-systolic volume and greater EF, as well as with a higher 24 h average heart rate and slightly depressed heart rate variability. This finding might be secondary to the

increase in sympathetic drive to the heart promoted by cocaine, with positive chronotropic and inotropic effects and a potential for specific adrenergic-driven necrosis.² Further studies are needed to test this hypothesis and evaluate the course of myocardial oedema after a prolonged abstinence.

Myocardial fibrosis is irreversible: it may result from a previous silent cardiac event and be recognised an 'ischaemic' pattern, which is evaluated by its localisation within a definite coronary artery territory, or a non-ischaemic pattern, which probably reflects different pathogenic mechanisms (toxic or inflammatory) in the individual subject.

We found that 68% of subjects presenting with a fibrosis had non-ischaemic patterns and 32% had ischaemic patterns. Single-drug addicts showed either pattern, while polydrug addicts showed a significantly higher prevalence of the non-ischaemic pattern, which was present in all subjects consuming both cocaine and ethanol. The combination of cocaine and ethanol, leading to production of the metabolite coca-ethylene via liver transesterification, blocks dopamine reuptake, favouring an increase in drug cardiac toxicity through non-ischaemic mechanisms.²⁶

Global ventricular function was found to be preserved, on average, while modest regional wall motion abnormalities were found, both by CMR and by echocardiography, in 40% of subjects. This finding was in agreement with previous observations by Ren *et al*, who described systolic impairment using the tagging technique in 32 cocaine addicts.²⁷

Minor ECG abnormalities were found in only 43% of subjects with myocardial oedema and in 63% of subjects with myocardial fibrosis, with some concordance of localisation with the site of either myocardial oedema or fibrosis. The ECG test was always negative, indicating no signs of microcirculatory dysfunction during stress.

Echocardiography disclosed only minor regional left ventricular abnormalities, which were probably due to the modest extent of underlying pathological processes, evident at CMR examination.

Biomarkers of necrosis and cardiac involvement, such as ultrasensitive troponin and NT-proBNP, were found to be substantially negative, probably because drug withdrawal occurred at least 2 days before blood sampling. A trend towards higher troponin in subjects presenting with oedema was found, indicating a possible recent exposure to the drug with subsequent cardiomyocyte damage. Finally, no arrhythmic burden was evident from 24 h Holter recordings.

Limitations

The small sample size suggests a need for confirmation through larger population studies. Moreover, 25% of the subjects who initially enrolled refused the CMR study, probably because of the psychiatric comorbidity. Self-reporting on duration of cocaine addiction, modality, dose and time of last consumption might be inaccurate because of the social stigma surrounding the use of cocaine. For this reason, this information was collected by a trained psychiatrist. In this study we enrolled consecutive asymptomatic cocaine addicts without any selection, excluding only patients with previous history of cardiac symptoms or disease. We included also polydrug abusers (53% of our patients) and patients with HCV or HIV infection (20%). The chronic consumption of multiple drugs as well as the HCV and HIV infection may be cause of myocardial damage and be considered confounding factors. Lossnitzer *et al* demonstrated a high prevalence of fibrosis in patients with liver cirrhosis of alcoholic and viral aetiology.²⁸ Yet, the presence of myocardial inflammation was demonstrated in patients with HIV infection.²⁹ However,

these confounding factors did not alter the major results of this study because none of the enrolled subjects was cirrhotic and only two patients with viral infection had fibrosis. Moreover, we found signs of myocardial damage in 9/16 single-drug cocaine addicts without viral infection. Finally, both polydrug abuse and exposure to viral agents are characteristic of cocaine addiction and might be considered as concomitant factors in cocaine-induced heart disease.

Coronary CT angiography was performed only in patients with an ischaemic pattern of LGE. The presence of coronary artery disease was not completely excluded in the remaining patients. However, the younger age of the population and the negative exercise stress test reduces the probability of their having significant coronary artery disease.

Finally, our results, obtained in cocaine addicts, with a psychiatric diagnosis, attending for rehabilitation, may not be applicable to most recreational ('weekend') cocaine users.

In conclusion, we found a high prevalence of cardiac damage in asymptomatic cocaine addicts. This may indicate the need for screening in long-term users, even when they are asymptomatic. Cardiac structural involvement may precede cardiac events and become manifest later in life.

Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the ethical committee of Pisa, Italy.

Provenance and peer review Not commissioned; externally peer reviewed.

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